New methods in chiral synthesis

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To my mother, father and family for their support and belief

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Abstract

Solid phase organic chemistry has enjoyed a resurgence of interest following intense research activity in combinatorial chemistry. Despite the range of reactions amenable to operations in the solid phase, some aspects of work in the area are still limited. For example, the use of recyclable resin-bound auxiliaries to effect asymmetric transformations have not been exploited fully. Therefore, the development of such solid supported reagents remains a synthetical challenge. We chose to work with oxazolidinones as versatile auxiliaries and selected α-alkylation as the model reaction to be studied. Thus, the object of this thesis can be summarised as *"the synthesis and investigation of a resin-bound oxazolidinone and its efficacy in asymmetric alkylation reactions"*.

The first part of the thesis describes the synthesis of three oxazolidinones from readily available amino acid derivatives over 2-5 steps, in reasonable overall yields.

The second part of the work deals with the methods used to immobilize the oxazolidinones onto solid supports. Merrifield resin-bound auxiliary was synthesized via nucleophilic displacement in fair yield. Subsequent solid phase *N*-acylation with this polymeric reagent was attempted. The alternate use of the Mitsunobu reaction for immobilization was investigated using a model compound. The effectiveness of the two methods are detailed.

The final part of the thesis illustrates the attempted optimization of the alkylation reaction in solution phase. It was found that an increase in reaction temperature to 0°C is necessary to effect alkylation at a reasonable rate, but the instability of the lithium enolate at this temperature can seriously reduce the yield and recycling

potential of the resin-bound oxazolidinones. The use of additives and other enolates to circumvent this problem is examined.

Finally, the use of *N*-acyloxazolidinones as transferable ligands in Cu(I) mediated conjugate addition reactions was attempted. The results obtained are reported within this thesis.

Abbreviations

$[\alpha]_D$ - optical rotation

Bn - benzyl

Boc - *tert*-butyloxycarbonyl

Bu - butyl

i-Bu - isobutyl

t-Bu - *tert*-butyl

d - day

dba - dibenzylidene acetone

DBAD - di-*tert*-butyl azodicarboxylate

DCM - dichloromethane

d.e. - diastereomeric excess

DEAD - diethyl azodicarboxylate

DIPEA - diisopropylethylamine

DMA - dimethylacetamide

DMAC - dimethylaluminum chloride

DMAP - dimethylaminopyridine

DMF - dimethylformaldehyde

DMPU - dimethylpropyleneurea

DMSO - dimethyl sulfoxide

DVB - divinylbenzene

e.e. - enantiomeric excess

eq. - equivalent

Et - ethyl

EtOAc - ethyl acetate

ES - electrospray

FAB - fast atom bombardment

Fmoc - 9-fluorenylmethyloxycarbonyl

FTIR - Fourier transform infrared

g - gram

h - hour

HPLC - high pressure liquid chromatography

J - coupling constant

LDA - lithium diisopropylamine

LHMDS or LiHMDS - lithium hexamethyldisilazane

Me - methyl

mg - milligram

MHz - megahertz

min - minute

mmol - millimole

Mp - melting point

MS - mass spectrometry

MTPACl - α-methoxytrifluoromethylphenylacetyl chloride

m/z - mass : charge ratio

NBS - *N*-bromosuccinimide

NCS - *N*-chlorosuccinimide

NEPIS - *N*-ethyl-5-phenylisoxazolium-3'-sulphonate

NMP - *N*-methylmorpholine

NVOC - 6-nitroveratyloxylcarbonyl

OTf - triflate

PEG - polyethylene glycol

PM - portioning and mixing

Ph - phenyl

ppm - part per million

Pr - propyl

i-Pr - isopropyl

PS - polystyrene

R_f - retention factor

r.t. - room temperature

S_N1 - unimolecular nucleophilic substitution

S_N2 - bimolecular nucleophilic substitution

TBDM or TBS - *tert*-butyldimethyl

TBDP - *tert*-butyldiphenyl

TFA - trifluoroacetic acid

Th - thienyl

THF - tetrahydrofuran

tlc - thin layer chromatography

TMEDA - tetramethylethylenediamine

TMS - trimethylsilyl

$TrisN_3$ - triisopropylbenzenesulfonyl azide

uv - ultraviolet

VLSIPS - very large scale immobilized polymer synthesis

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Chapter 1: Introduction

1.1: Background

Traditionally, bioactive lead compounds are discovered by a variety of means including serendipity, rational drug design[1] and random screening. Random screening has been particularly useful as a tool, but the success rate is low and the process is time consuming. Recently, new trends in the search for novel therapeutic agents have focused on the preparation of chemical libraries. This area of research is collectively known as combinatorial chemistry[2-26].

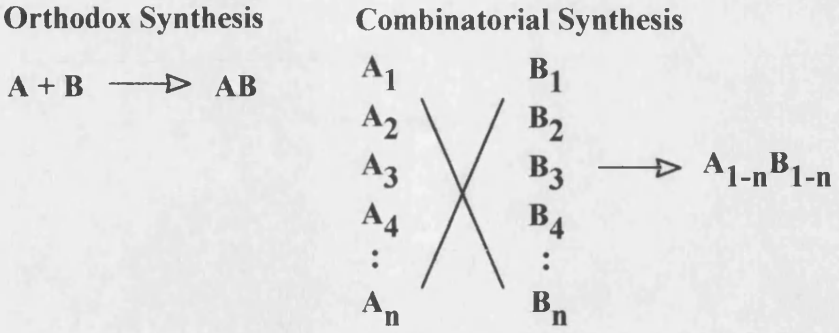
Since its birth in 1994, well over two hundred articles and seventeen books[27] have been published on this subject, and the number is set to increase as universities and industries invest more time and effort into this area of research. Huge financial rewards await the successful application of combinatorial synthesis to drug discovery. Typically, the prospect of such rewards encourage optimism, but thus far the results are still in the balance.

1.2: Combinatorial Chemistry

1.2.1: What is combinatorial chemistry: A definition

Combinatorial synthesis permits the efficient preparation of large numbers of structurally distinct molecules. Not surprisingly, some people view combinatorial chemistry as the science of efficient divergent synthesis[9]. Thus, compounds can be prepared simultaneously by combining a set or sets of chemical building blocks (or monomers) in just a few steps (Figure 1). The syntheses can take place in the same reaction vessel as a mixture, or individually in parallel, using semi-automated procedures.

Figure 1: Contrast between combinatorial chemistry and orthodox chemistry



The set of compounds produced is called a library. In a multistep combinatorial synthesis the size of the library "*N*" is determined by the number of monomers "A" or "B" used per reaction and the number of reaction steps "x". If the number of monomers used remains unchanged in each reaction step, then $N = A^x$ or B^x. If the number of monomers for each step varies then $N = ABCD$ for a four step synthesis.

Table 1: The power of combinatorial method in library generation

	Units	Library size		Units	Library size
Set of 20	20^3	8,000	Set of 1000	1000^3	1 Billion
	20^4	160,000		1000^4	1 Trillion
	20^5	3.2 Million		1000^5	1 Quadrillion

The population of the library increases exponentially even with a relatively small number of monomers (Table 1). Therefore, a modern synthetic chemist can access a whole spectrum of compounds using this technique. Such approaches stand in sharp contrast to the traditional activity of synthetic chemistry, wherein reactions are typically performed on an individual basis in the hope of obtaining single, well-defined products. In today's competitive market, pharmaceutical companies are

looking to harness the power of combinatorial synthesis to give them their number one best-sellers.

Despite this great potential, one has to design and plan combinatorial syntheses with care. For example, it will be impossible to synthesize and test all compounds with a molecular weight of 750 daltons, the so-called "small" organic compounds. The figure is estimated at 10^{200} **[28]**. Therefore a selection procedure is needed for both the products and the building blocks used. This issue of design and implementation of combinatorial synthesis is discussed in several excellent reviews**[3, 6]**.

1.2.2: Solid Phase Synthesis in Organic Chemistry

In principle, combinatorial synthesis can be performed both in solution and in the solid phase. A comparison between the two methods is shown below (Table 2 and 3).

Table 2: Pros and cons of solution phase combinatorial synthesis

Advantages
• All organic reactions can be applied-in theory
• No adaptation of reaction conditions is needed
• Do not need linking to and cleaving from the support
• Unlimited amount of products can be produced
Disadvantages
• Purification is more complex. Excess reagents cannot be used to drive reactions to completion
• Automation of isolation and purification procedures is troublesome

The simple workup associated with solid phase is particularly attractive, where multistep syntheses are involved. This advantage outweighs many solution based reactions where lengthy chromatography or crystallization is required. The ability to drive reactions to completion reduces reaction time. While the ease of automation

reduces labour cost. These inherent features of solid phase make this approach suitable for combinatorial synthesis in industry.

Table 3: Pros and cons of solid phase combinatorial synthesis

Advantages
• Reactions can be driven to completion by using excess reagents without separation problems
• Products can be purified by simple washing and filtration procedures
• Automation of reaction sequences is possible
• Pseudo-dilution effect**[29]**
Disadvantages
• Development required for optimized synthesis
• Additional time and cost in synthesizing desired polymeric support
• Extra reaction steps are required for linkage to and cleavage from the support
• Availability of supports and linkers limit the executable range of chemistry
• Quantity of product prepared depends on the loading of the support
• Methods for monitoring of reaction are not well developed

1.2.3: History of Solid Phase Synthesis

Solid phase synthesis began in early 1960s by pioneers such as Merrifield**[30]** and Letsinger**[31,32]**. For example, in 1963, Merrifield introduced his classic "solid phase peptide synthesis methodology", which initiated research in this area. In his original work, a N^{α}-protected C-terminal amino acid was attached to chloromethylated polystyrene-divinylbenzene. The polymer functions both as an anchor as well as a protecting group for the carboxyl group of the amino acid. After removal of the N^{α}-protection, the next N^{α}-protected amino acid is coupled and the process is repeated until the desired peptide is assembled. This approach by-passed the difficult separation of peptides after each coupling sequence. The simplicity of the methodology soon led to the development of an automated peptide synthesizer**[33]**.

These successes did not go unnoticed by the wider chemistry community. A flurry of activity followed into the early 1980s in the Solid Phase Synthesis (SPS) of organic molecules. Frechet**[34]**, Leznoff**[35-42]** and Patchornik**[43]** were particularly active in the early stages of SPS. A variety of synthetic applications and transformations compatible with solid phase approach were unearthed. The early reviews[**34-36,44-46]** on SPS classified the functionalized polymers into five groups: reagents, catalysts, carriers for separation and carriers for organic synthesis. Early practitioners of SPS noticed its most distinctive advantage concerned the ease of processing reagents and products. For example, workup is reduced to filtration and washing of the polymeric support. Apart from these advantages, as mentioned before, other more general benefits (not just for combinatorial synthesis) are listed below (Table 4).

Table 4: General benefits of solid phase synthesis

Benefits
• Ability of the polymer to be recovered, regenerated or recycled. This is important when the supported material is scarce or expensive.
• Polymer supported toxic and malodorous materials are safer and easier to handle. More environmentally friendly.**[47,48]**
• The reactivity of an unstable reagent or catalyst may be attenuated when supported on a polymer.**[49]**
• The automatic removal of the spent reagent is facilitated by virtue of its attachment to an insoluble polymer. The spent reagent can be recovered and reconverted back to the original reagent.**[50]**

In spite of these benefits, the field of SPS remained largely under-used at this time. The major obstacle to progress being the lack of adequate analytical techniques for characterizing insoluble polymers and the monitoring of reactions. Titration of reactive functionalities, gravimetric monitoring of reactions, elemental analysis and infrared spectroscopy**[51]** were mainly used as analytical controls.

1.2.4: History of Combinatorial Chemistry

Despite limited activity, several land mark peptide syntheses using combinatorial principles were reported and these ushered in a new dawn in the area of chemistry. For example, in 1984, Geysen introduced the Multipin Method**[52,53]**. He replaced traditional Merrifield resins with reusable polyacrylic acid grafted polyethylene pins. These pins were 40 mm in length and 4 mm in diameter. The pins were attached to a supporting block and arranged in an 8 X 12 microtitre plate format. The microtitre plates acted as reservoirs for reaction solutions and for washing solutions. A diamine spacer was added to the acrylic acid to increase mobility and to provide a reactive "handle" for attaching the peptide. Thus, it was shown that up to 96 peptides can be synthesized simultaneously.

One year later, Houghton used his "Tea-Bags" method**[54]** for the synthesis of peptides. This approach has the capacity to synthesize more peptides than the Multipin method. Although the latter can be made to exceed its formal limitation by generating a mixture of peptides on each pin**[55]**, this presents practical problems and the teabag method is in fact, preferable.

In the Houghton Tea-Bag procedure, a polypropylene mesh bag with the dimensions of 15 X 20 mm and a mesh size of 74 μm is filled with resin beads to which the first amino acid becomes bound. The size of the mesh is too small to let the resin beads out, but large enough to let the solvent and reagents into the bag. Many teabags can be placed in the same reactor for common synthetic steps. Hence, much time and effort are saved when preparing large peptides libraries. This method has been successfully applied to many combinatorial syntheses**[56,57]**.

The productivity of these methods is greatly enhanced by the Portion-Mixing (PM) technique pioneered by Furka**[58-62]**. This technique is also known as "split and mix technology"**[63]**, "one-bead, one peptide approach" or the "divide, couple and recombine (DCR) process**[56]**.

Theoretically, the PM technique uses the same strategy as Merrifield's solid phase method. The only difference is the replacement of the coupling procedure by the following operations.

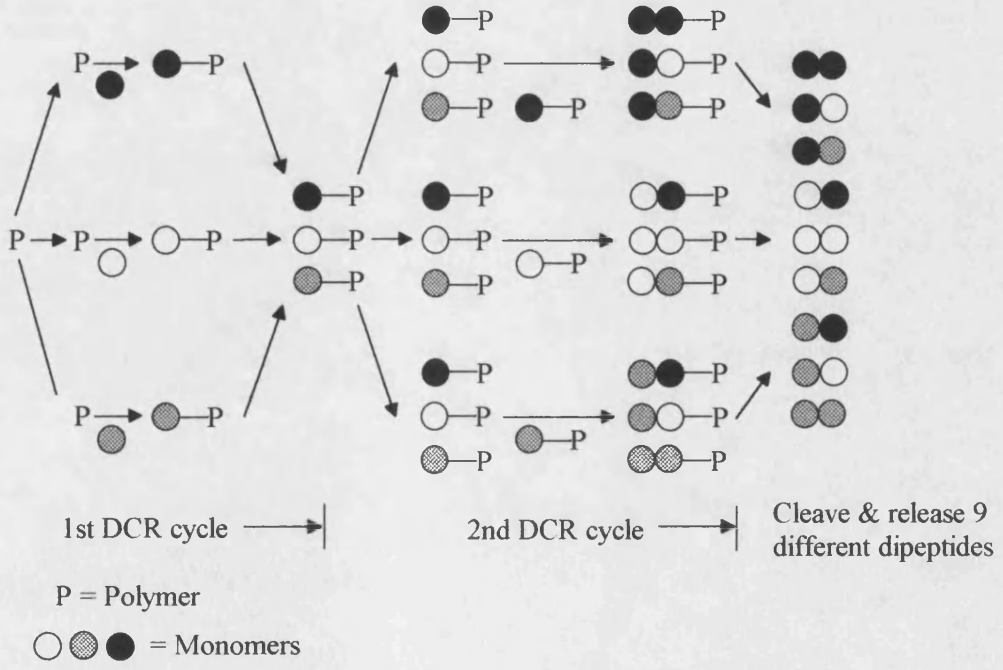
1: Division of the resin beads into equal portions, before the coupling.

2: Coupling.

3: Mix the portions of resins.

The number of portions is determined by the number of building blocks employed. In the case of peptide libraries, the number of amino acids is intended to vary in one position, while the number of portion and mix cycles represent the residue number in the peptide. For a 3 x 2 library containing 9 dipeptides, the synthesis goes as follows (Figure 2).

Figure 2: The principle of the Portioning & Mixing (PM) technique



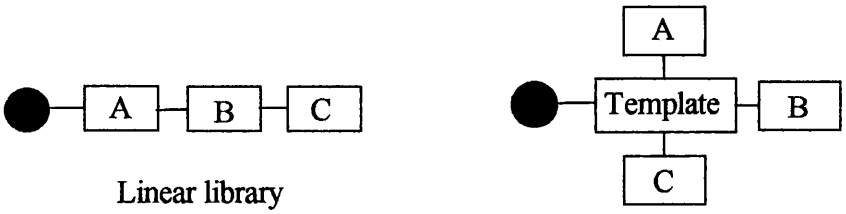
In the first cycle, the resin beads are divided into 3 equal portions. The portions are coupled with their designated *N*-protected amino acids. One type of *N*-protected amino acid is associated with each portion. The resin beads from the three portions are then mixed again. The second cycle starts with the mixture being divided into 3 equal portions. After *N*-deprotection, each polymer-bound amino acid is coupled with a second *N*-protected amino acid. Then the products are mixed again, the cycle is terminated and finally the dipeptides are released from the resin (Figure 2). The PM technique has two distinctive characteristics applicable to other libraries beside those of peptides. The first feature is the ability to synthesize products containing all the possible combinations of monomers. The other feature is the formation of only one type of compound on any one bead. The PM method has the added bonus of by-passing the problem of variable reaction rates, since there is only one reactant present in the reaction vessel at any given time.

1.2.5: Library Nomenclature and Classes of Library

Many mathematical approaches have been attempted to describe the construction of a library. In 1997, Maehr**[64]** used a detailed set theory to describe the construction of a library and its structure. He developed a flexible descriptive terminology applicable to both solid and solution phase operations and applied it to describe the synthesis of a solution library containing bioactive lead compounds**[65]**. A detailed discussion is outside the scope of this thesis, but the interested reader should consult the original paper for a full explanation.

The types of library constructed can often be grouped into two classes: linear and template (Figure 3).

Figure 3: Different type of libraries



Linear library

Template library

Linear libraries are naturally defined as A-B-C type, viz peptide libraries, but in template libraries, while no connection exists between A, B or C, all three reactants are all connected to a multi-functionalised template in the final product. The template library is used where maximum diversity is required for the compounds.

1.2.6: Other Solid Phase Supports

Combinatorial synthesis can made to occur on other solid phases apart from the traditional resin beads. One example is the use of multipins, previously discussed. Other examples of different solid phases include the "Winks" system**[66]**. Winks are porous polyethylene disks with a diameter of 7 cm and thickness of 3 cm. After appropriate functionalization and derivatization, the Winks provide a highly hydrophilic and accessible environment for peptide elaborations.

In 1991, workers at Affymax introduced the VLSIPS (very large scale immobilized polymer synthesis)**[23,67]** technology or light-directed spatially addressable parallel chemical synthesis. This technology utilized a combination of photolithography and solid phase synthesis. The synthesis takes place on a glass support derivatized with amino groups, protected with 6-nitroveratyloxylcarbonyl (NVOC) groups**[68,69]**. During reaction, the protected or "masked" amino groups are "unmasked" by UV irradiation (at 365 nm) for further elaboration. The VLSIPS technique consumes

very small quantities of reagents, but it is able to produce a large number of products on a very small area.

Solid phase synthesis on paper also is possible. Frank and Doring**[70]** prepared peptides using a packed column of labelled paper disks. Later, Frank introduced "Spot Synthesis"**[71]** where the peptides are prepared simultaneously on different areas of the same paper sheet. The main drawbacks are the hydrophilicity of cellulose, high acid lability and the limited range of chemistry compatible with paper. Gao and Esnouf**[72]** replaced the paper with a polymeric membrane made from inert polyvinylide fluoride. After derivatization, spot synthesis of peptides can be performed rather like that on paper.

1.2.7: Analysis of Reactions

The inability to monitor and analyse reactions on solid phase still remains an obstacle. In general, technological advances have focused on improving existing methods. Thus IR analysis**[51,73]** has been used since the early stage of SPS to monitor reactions by observing changes in the absorptions of functional groups involved. Most commercially available polystyrene-divinylbenzene (PS-DVB) supports give good spectra from KBr discs, apart from the polyethylene glycol (PEG) PS-DVB support, which gives weaker absorptions**[74]**. The increase in the detection sensitivity has led to single bead FT-IR microspectroscopy**[75-81]**, which obviously only needs a single bead. The use of NMR spectroscopy has increased in popularity due to improved technology. Gel-phase ^{13}C carbon NMR**[82-86]** and particularly Magic Angle Spinning Nuclear Magnetic Resonance MAS NMR**[87-90]** have found widespread applications. Studies **[91,92]** showed that Tentagel, Wang and Rink

resins all give acceptable MAS proton spectra with Tentagel being the best. Polystyrene resins produced the worst spectra, due to the closeness of the bound compound to the polymer's backbone, resulting in a much reduced fluidity. ^{19}F, ^{31}P and ^{15}N NMR spectra have been used to monitor reactions**[93-96]**. The benefit here is the simple nature of the spectra due to the absence of polymer signals. Mass spectrometry techniques such as matrix assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS)**[97-99]**, time-of-flight secondary ionisation mass spectrometry (TOF-SIMS)**[100]** and electrospray ionisation mass spectrometry (ESI-MS) **[101]** are extremely sensitive and can detect compounds at picomole to femtamole levels. Simple preparation of samples and possible automation makes these techniques powerful tools in monitoring, but also in the identification of library compounds. However, quantification by MS is very difficult to achieve.

Classical techniques like elemental analysis**[102]** has been re-investigated and shown to be suitable for polystyrene- and TentaGel-bound organic compounds. However, other older methods such as titration of functional group and colour tests**[103-105]** are equally informative and more rapidly carried out.

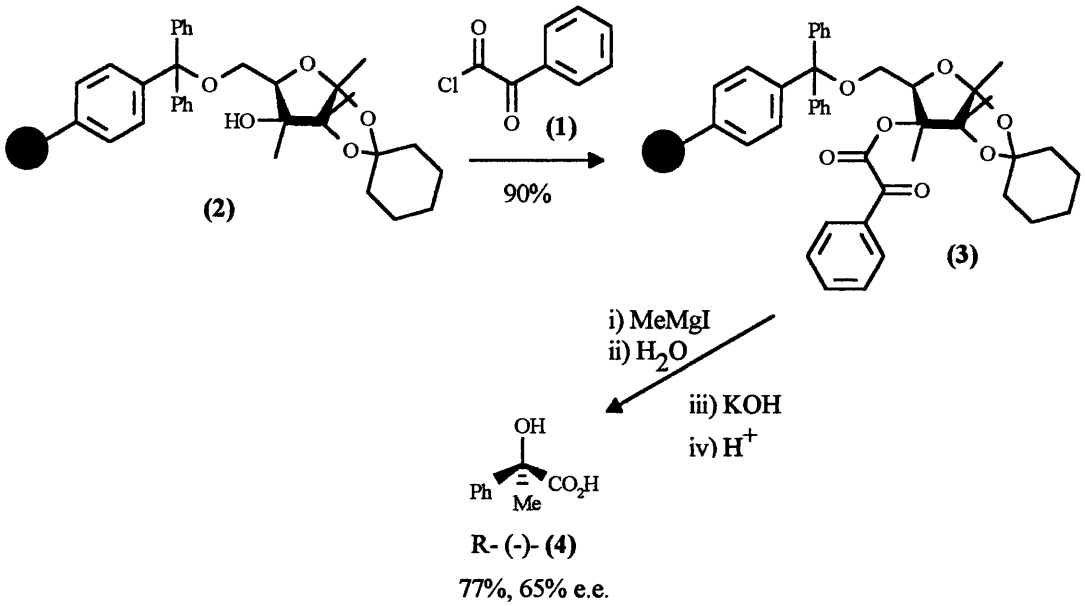
1.2.8: Solid Phase Organic Chemistry in the 1990s

After successes in forming peptides and oligonucleotide libraries, the focus has shifted towards the generation of small organic molecules libraries**[106-108]**. This has led to a resurgence in solid phase synthesis to provide the necessary "tools" for library construction. The term solid phase organic synthesis (SPOS) was coined to describe the evolution of SPS to meet the demand of combinatorial organic synthesis (COS). An increasing number of classic organic reactions**[109-115]** have been

successfully adapted to solid phase processes. The solid phase synthesis of benzodiazepines illustrates the rapid progress in SPOS. In 1974, Camps[116] first synthesized benzodiazepine derivatives on a solid support in 32-64 % yield. Eighteen years later, Ellman and Bunin[117] synthesized a benzodiazepine library with yields in the region of 80-100 %. Despite the tremendous progress being made in SPOS, the repertoire of reactions available to chemists is still limited. A particularly unexplored and overlooked area concerns the use of polymer supported auxiliaries. The ease of purification and the possible benefit of recycling the auxiliary represent an attractive concept. However, only a handful of examples of their uses in asymmetric synthesis have been reported. The earliest example came from the work of Kawana and Emoto[118].

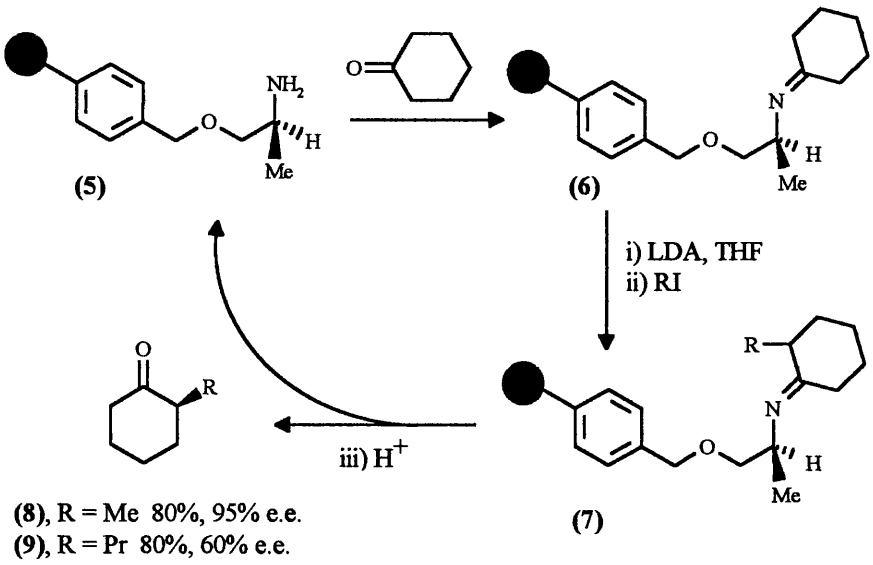
Phenylglyoxyl chloride **(1)** was attached onto a polymer-bound xylofuranose derivative **(2)**. Subsequent treatment of the polymeric reagent **(3)** with methyl magnesium iodide, followed by hydrolysis furnished the *R*-(-)-atrolactic acid **(4)** in 77% yield and 65% optical purity (Scheme 1).

Scheme 1: Earliest example of a polymer bound auxiliary in asymmetric synthesis



Both values were higher than the solution phase equivalent of 68% yield and 53% optical purity. The auxiliary **(2)** was recycled and used again to give a lower values of 73% and 58%, respectively; these decreases in efficiency are probably due to the mechanical degradation of the resins. Several examples of solid phase alkylation of cyclohexanone were published after a seven year gap. Leznoff and coworkers**[37,38]** prepared (*S*)-2-methylcyclohexanone **(8)** in 80% yield and 95% e.e. and (*S*)-2-propylcyclohexanone **(9)** in 80% yield and 60% e.e. (Scheme 2).

Scheme 2: The stereoselective synthesis of α-substituted cyclohexanone

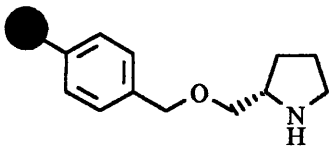


Here, the polymer-bound (*S*)-2-amino-1-propyl group **(5)** was recycled and used to give products with unchanged e.e., but reduced capacity. On the other hand, Frechet and coworkers**[119]** utilised a polymer-bound (*R*)-phenylethylamine to make (*S*)-2-methylcyclohexanone **(8)** in 61% e.e.. The polymer-bound auxiliary was recycled successfully.

In 1981, Meyers investigated the use of polymer-bound oxazolines**[120]**, but problems with product hydrolysis rendered this approach unattractive.

More recent work in this area is by Kurth and coworkers**[121,122]** on iodolactonization reactions. Kurth demonstrated that nonracemic 3,5-disubstituted γ-butyrolactones can be prepared from a (*S*)-2-pyrrolidine-functionalized polystyrene resin **(10)** (Figure 4). The key step is the stereoselective α-allylation of the chiral amide on solid support. This is followed by lactonisation in solution phase after cleavage. More importantly, the reaction selectivities are comparable to those of the complementary solution phase reactions and the auxiliary can be recycled successfully.

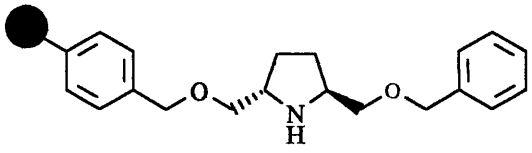
Figure 4: Resin-bound (*S*)-2-pyrrolidine auxiliary



(10)

Two years later, Kurth and coworkers developed a second generation pyrrolidine-based auxiliary**[122] (11)**, which has a C2 symmetry (Figure 5). This auxiliary exhibits a higher selectivity and it could also be recycled with no loss of chemical yield or stereoselectivity.

Figure 5



(11)

Important conclusions can be drawn from the previous work. Firstly, the product must be easily attached and cleaved to maximize the chance of reusing the solid supported reagent. Secondly, the auxiliary mediated reactions must be mild, efficient and "clean" with little to no side products. This minimizes the deactivation

of the auxiliary through resin bound impurities. For the work which forms the basis of this thesis, a survey of commonly used auxiliaries was performed with these simple guidelines in mind. A class of auxiliaries belonging to the oxazolidinone family was found to fulfil all these requirements. These versatile auxiliaries effect a wide range of asymmetric transformations with excellent yields and control. Their chemistry will be discussed in the next chapter.

Chapter 2: Oxazolidinones: A Review

2.1: Introduction

For a solid-supported auxiliary to be successful, it must effect reactions which are reliable and high yielding. In addition, the condition for the recovery of the auxiliary must be mild. There are many auxiliaries which fulfil the above criteria, but few can rival the repertoire of reactions covered by a class of auxiliaries known as the oxazolidinones.

Oxazolidinones are crystalline compounds that effect a wide range of asymmetric transformations with excellent yields, stereocontrol and a minimum of side reactions. These include alkylation, aldol and Diels-Alder reactions which constitute some of the most fundamental approaches to carbon-carbon bond formation. Their versatility, ease of preparation and recovery from reactions has ensured their popularity with modern organic chemists. This popularity is reflected in the ongoing interest in the development of more efficient oxazolidinones**[123]** and the investigation of novel chemical transformations**[124]**. The adaptation of this methodology to solid phase synthesis will extend its synthetic application enormously. Furthermore, it is often the case that modifications to the oxazolidinones can be effected by well established methods. It is therefore appropriate that the chemistry of the oxazolidinone should be reviewed before summarizing this specific research proposal. Thus, the rest of this chapter serves to illustrate the elegance and power of this methodology.

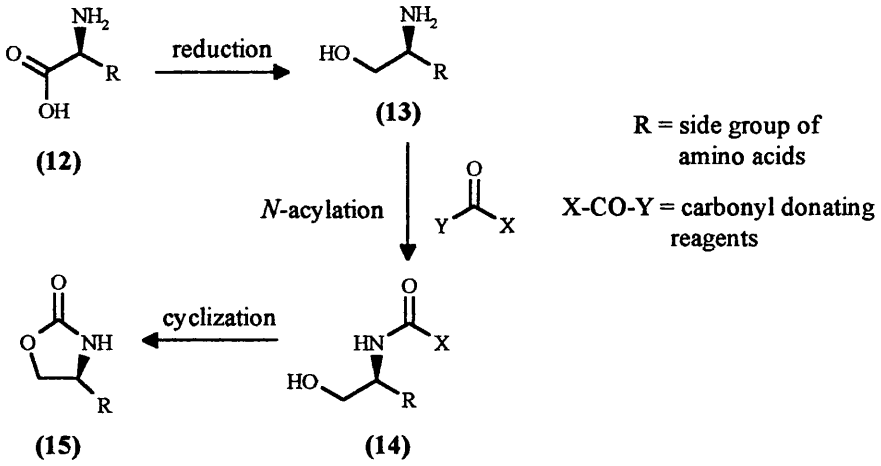
2.2: Preparation of Oxazolidinones

Oxazolidinones can be synthesised from chiral amino alcohols and carbonyl donating reagents. The starting amino alcohols are readily prepared from naturally

occurring α-amino acids and the chirality of the substrate (if any) is translated into the product oxazolidinones (Scheme 3).

Traditionally, phosgene**[125-6]** was used for transforming **(13)** to **(15)**, but it has now been replaced by safer alternatives such as triphosgene**[127-9]**, diethyl carbonate**[130]** and carbonyldiimidazole**[131]**. While carbamates, derived from isobutyl or phenyl chloroformate**[132]**, trichloromethyl chloroformate**[133]**,

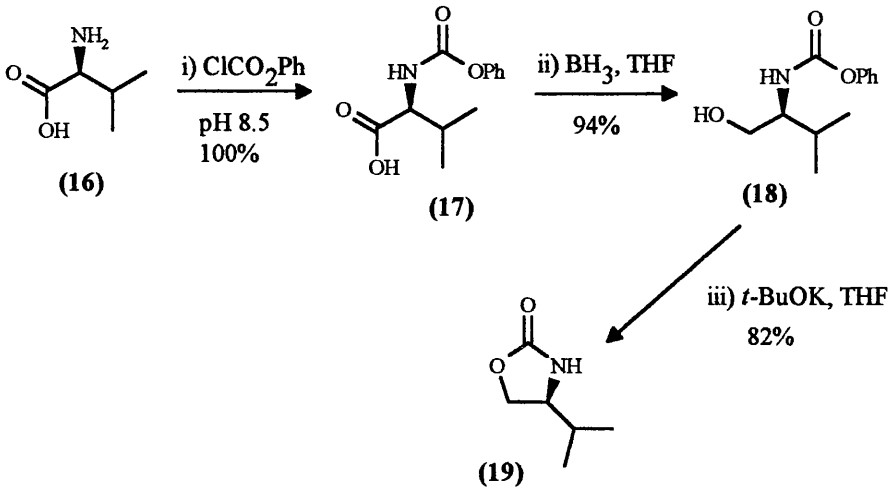
Scheme 3: Basic approach to the synthesis of oxazolidinones



trichloromethyl acetic anhydride**[134]**, dichloromethyl chloroformate**[135]**, ethyl chloroformate**[136]**, and di-*tert*-butyl dicarbonate**[137-9]** can also be cyclised to the heterocycle under mild basic conditions. Other procedures utilise a two step reaction involving carbon disulphide initially, followed by oxidation with hydrogen peroxide**[140]**.

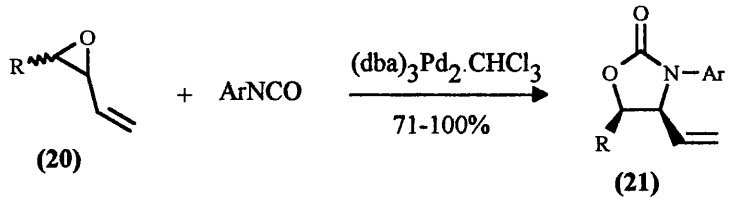
A specific example is that of the 4-isopropyl derivative **(19)**, which is synthesized in 3 steps and in an overall yield of 77% from (*S*)-valine **(16)** (Scheme 4).

Scheme 4: Synthesis of (*S*)-4-isopropyloxazolidinone



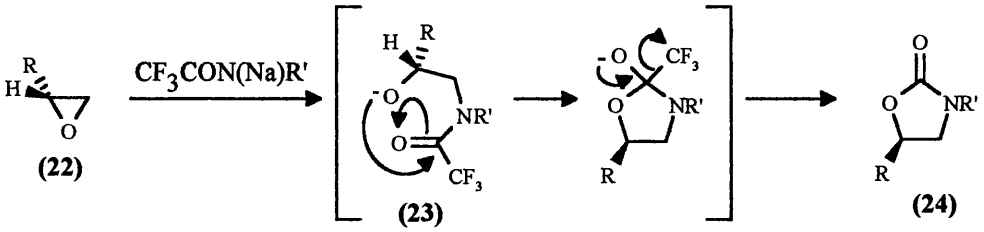
Although this is the preferred and most straightforward approach to oxazolidinones, other routes are available. One such route is the use of epoxides, which may be reacted with isocyanates. In the case of the reactions of aryl isocycanates with vinyl epoxides **(20)**, the coupling procedure is mediated by palladium catalysts**[141]**. Here the products **(21)** tend to be those having the (*Z*)-stereochemistry, regardless of the nature of the epoxide used (Scheme 5).

Scheme 5



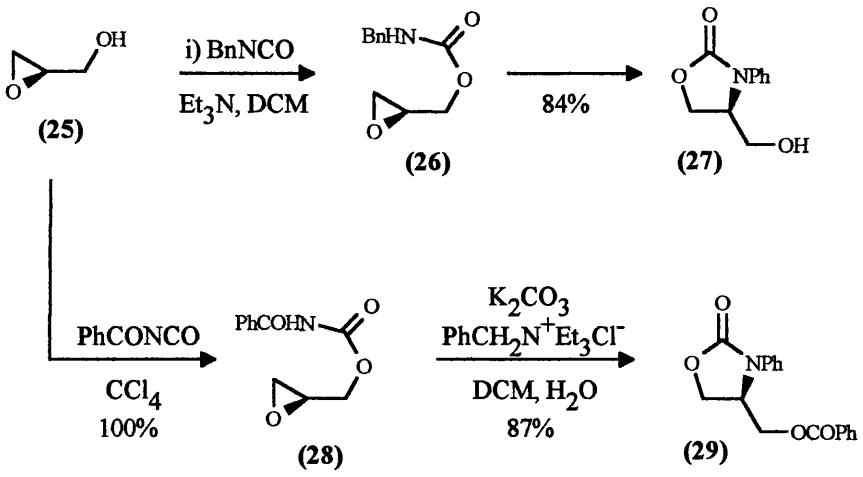
Epoxides **(22)** can also be ring-opened by the sodium salts of trifluoroacetamides**[142]** initially to give intermediates of the type **(23)**, that then cyclise to *N*-oxazolidinones **(24)** (Scheme 6).

Scheme 6



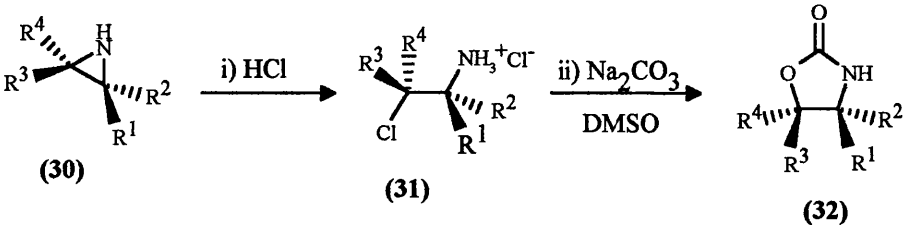
Enantiomers of glycidol**[143-4] (25)** can be reacted with benzyl or benzoyl isocyanate to give oxazolidin-2-ones (Scheme 7). This offers an alternate starting materials to (*S*)-serine.

Scheme 7



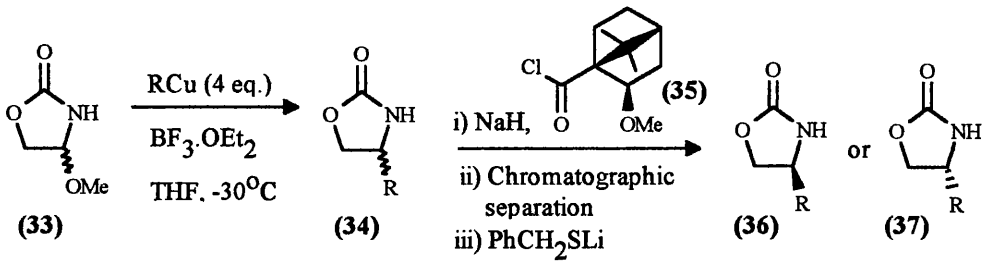
Aziridines **(30)**, like epoxides, can be employed as starting materials in the formation of the oxazolidinones. The aziridines are initially converted into a chloroamine **(31)** through reactions with hydrogen chloride. Condensation with sodium carbonate then yields the isomerically pure oxazolidinones**[145-7] (32)** (Scheme 8).

Scheme 8



A versatile route to both enantiomers of 4-substituted oxazolidinones has been reported by Kunieda[148]. The 4-methoxy-2-oxazolidinone **(33)** was treated with a wide range of organocuprates complexed with BF_3 to give the 4-substituted heterocycles **(34)**. *N*-Acylation with 1-apocamphanecarbonyl chloride **(35)**, followed by chromatographic separation and deacylation affords the chirally pure products **(36)** and **(37)** in 27-99% yield (Scheme 9).

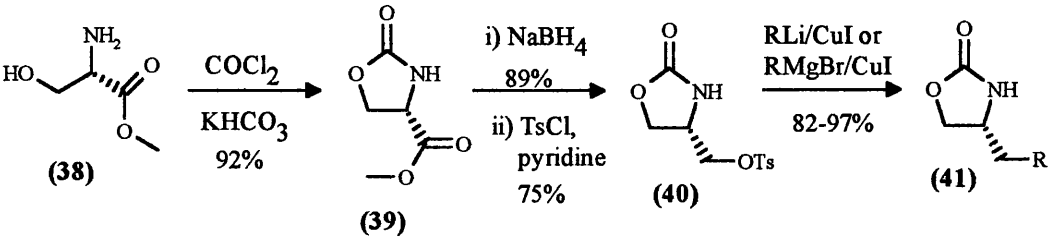
Scheme 9



R = Me, *i*-Pr, *t*-Bu, Ph, vinyl, α-naphthyl, $C_6H_{11}CH_2$-

A similar approach is used by Sibi[149] in his synthesis of 4-substituted oxazolidinones **(41)** . After the ring formation, the ester group **(39)** is reduced into an alcohol and then converted into a tosylate **(40)** . Displacement of the tosylate by an organocopper reagent affords the 4-substituted product **(41)** with retention of stereochemistry and in high yield (Scheme 10).

Scheme 10

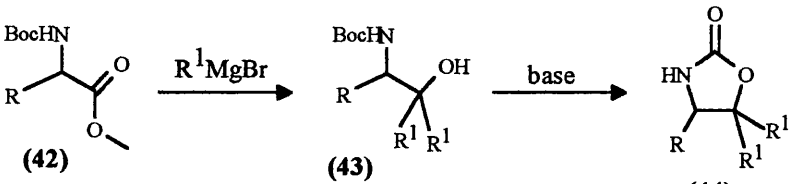


R = Ph, Bn, Me, Et, Bu, C_6H_{11}-, $CH_3OC_6H_4$-

4,5,5-Trisubstituted oxazolidinones **(44)** are more crystalline than their non-substituted counterparts and their added complexity directs bulky reagents to attack in an exocyclic manner. These heterocyclic compounds can be accessed by the

reaction of amino acid esters **(42)** with appropriate Grignard reagents**[139, 150-6]**. The protection of the nitrogen atom by a Boc group results in high yields in the first step and helps in the preservation of the chiral centres. Base induced cyclization of the *N*-protected amino alcohols **(43)** then furnishes the desired compounds **(44)** in good yields (Scheme 11).

Scheme 11



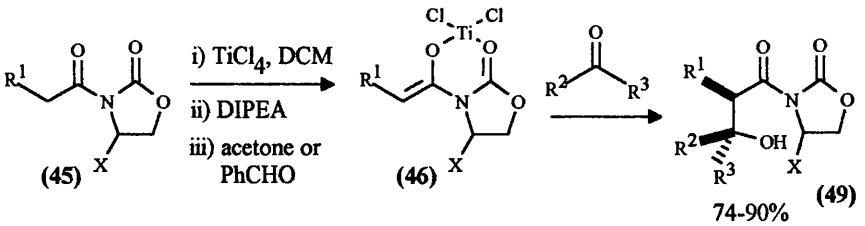
(42) **(43)** **(44)**

(*R*) or (*S*) *N*-protected amino acid esters

R^1 = 4-$CH_3C_6H_4$, Ph, Bn, Me, 2-naphthyl
R = *i*-Pr, Bn, Ph, 3-methylindolyl

Oxazolidinones can themselves be used as starting materials for more substituted oxazolidinones. The starting compounds may be chiral, in which case they often stem from α-amino acids. The sequence of reactions then requires the formation of a titanium enolate **(46)** and then acetylation with a carbonyl compound, such as acetone **(47)** or benzaldehyde **(48)** to give the aldol **(49)** (Scheme 12).

Scheme 12



(45) **(46)** **(49)**

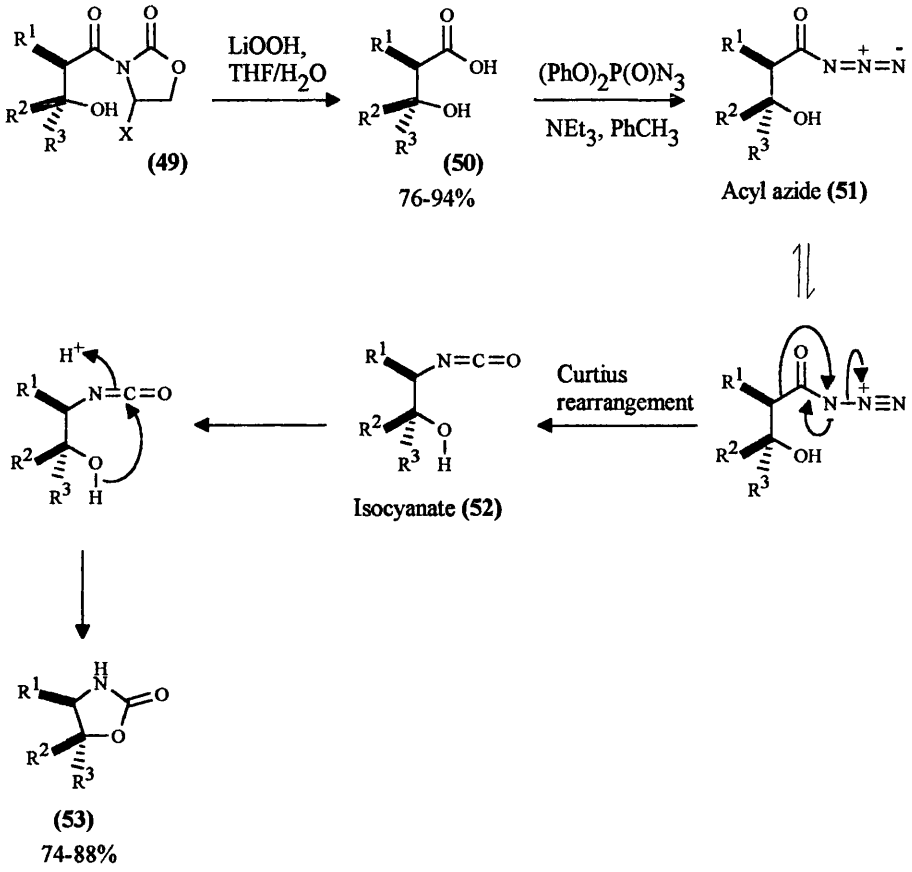
X = *t*-Bu, Bn
R^1 = Bn, Ph, 2-naphthyl

(47) R_2, R_3 = CH_3
(48) R_2 = Ph, R_3 = H

After oxidative hydrolysis, the resultant β-hydroxyacids **(50)** are converted into acyl azides **(51)** and subjected to a Curtius rearrangement. The resultant isocycanates

(52) are then quenched intramolecularly to afford the oxazolidinones **(53)** (Scheme 13).

Scheme 13

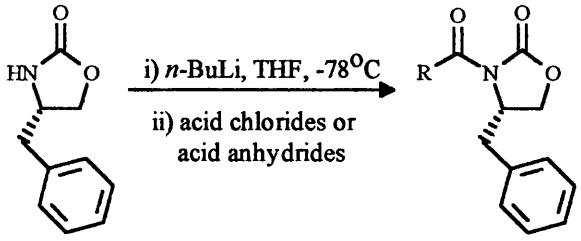


Other chiral natural or unnatural starting materials have been used in the construction of oxazolidinones. For example, terpenes**[157-9]**, carbohydrates**[160-4]** and certain 2-oxazolones**[165-7]**.

2.3: Formation of *N*-Acyloxazolidinones

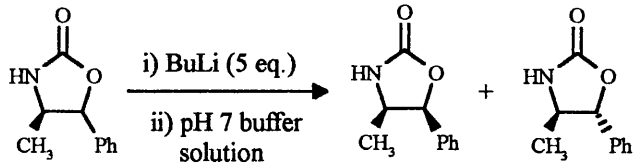
There are two main ways to attach *N*-acyl substituents onto oxazolidinones. Traditionally, the oxazolidinones are treated with a strong base such as *n*-butyl lithium and then reacted with acid chlorides**[168-9]**, or anhydrides**[170-1]** to afford the *N*-acylated products in high yields (Scheme 14).

Scheme 14



However, the use of excess strong base must be avoided for ephedrine derived oxazolidinones**[172]** as racemization can occur at the C5 position (Scheme 15).

Scheme 15

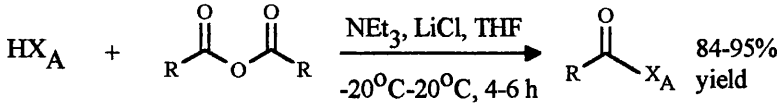


Either diastereomer **(54)** (4*R*,5*S*) 1:4 (4*R*,5*R*)**(55)**

Nevertheless, the risk of racemization is eliminated by employing a milder base such as triethylamine. This tertiary amine has been used in conjunction with a catalytic amount of DMAP and acid chlorides, or anhydrides, to give *N*-acyloxazolidinones **[164,173-4]**. However, this reagent system is not compatible with more polarizable thiazolidine-2-thiones derivatives as the DMAP also causes *N*-deacylation**[175]**.

The synthesis of *N*-acryloyl derivatives with *n*-BuLi is often accompanied by polymerization, which lowers the yield of product. The addition of magnesium salts as co-reagents**[176-7]** for the acid chlorides partially resolves this problem. A more satisfactory method**[178]**, however, involves the use of lithium chloride (1.1-1.2 eq.), triethylamine and an acid anhydride as the acylating reagent (Scheme 16). The role of the various salts in repressing polymerisation is not known for certain.

Scheme 16

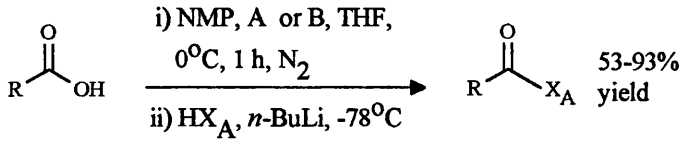


HX_A = Sultam and oxazolidinones derived from phenylalaninol, norphedrine and 1-amino-2-hydroxyindan

R = Et, $CMe=CH_2$, CH=CHMe

This method can be extended to alkynoyl derivatives**[179]**. Other procedures include the use of triethylamine/2-chloro-1-methylpyridinium iodide for *N*-acryloylation**[180]**. As for β,γ-unsaturated *N*-acyloxazolidinones, the use of *N*-methylmorpholine**[181]** as the base in the formation of mixed anhydrides is found to suppress isomerization and prevent racemization at the α-position (Scheme 17). Although its exact mode of action is uncertain.

Scheme 17



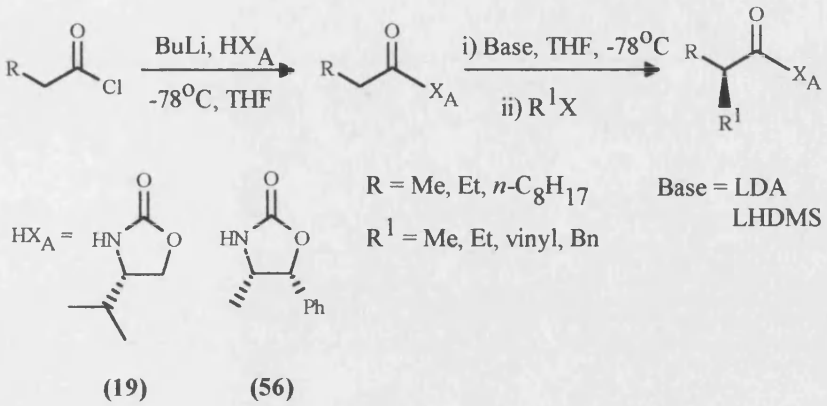
$R = CH_2, CH=CH_2, CH(Me)CH=CH_2, CH=CH_2$

A = *t*-BuCOCl B = *i*-BuCOCl HX_A = oxazolidinones derived from phenylalanine and norephedrine

2.4: Alkylation Reactions

In 1982, Evans**[182]** developed a powerful C-C bond forming method based on a chiral metal enolate system. High yields and excellent levels of asymmetric induction are observed in the alkylated products (Scheme 18) and Table 5. Complementary selectivity in the product is possible by the appropriate use of auxiliaries.

Scheme 18



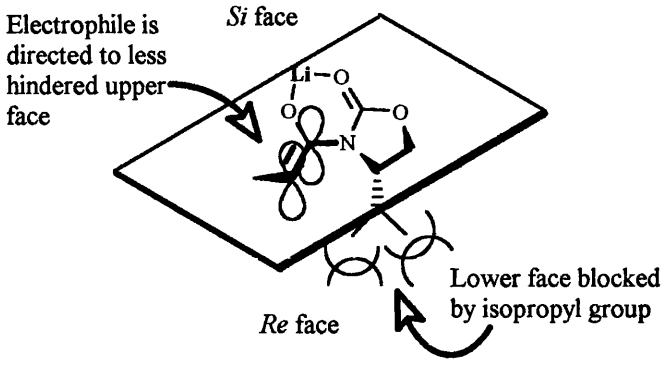
(19) **(56)**

Table 5: Results of stereoselective α-alkylation

Oxazolidinone	Electrophile	Yield of major diastereomer (%)
19	MeI	80
56	MeI	74
19	$PhCH_2Br$	98
56	$PhCH_2Br$	96
19	$H_2C{=}CHCH_2Br$	96
56	$H_2C{=}CHCH_2Br$	96

To account for the high selectivity**[183-4]**, one must look back at the structure of the enolate, which is formed by the treatment of *N*-acyloxazolidinones with LDA or sodium bis(trimethylsilyl)amide (NaHMDS). In fact the enolate has the (*Z*) geometry with a selectivity of >100:1, and freedom of movement within the enolate is restricted due to chelation. In this rigid form, the two faces of the enolate are made diastereotopic by the presence of a chiral centre at C-4 position. An attack of the electrophile from the same side as the C4 substituent is disfavoured due to steric hindrance, forcing the approach of the electrophile to the less hindered *si* face of the enolate (Figure 6).

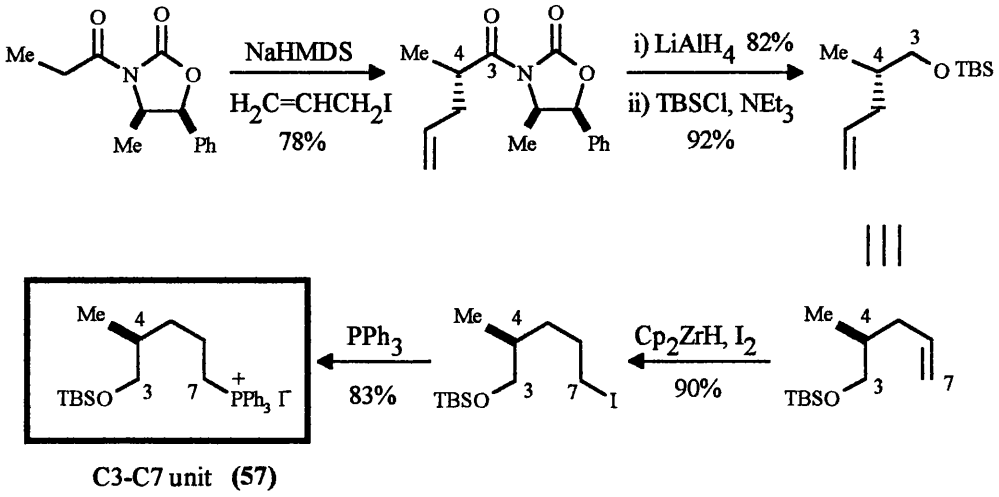
Figure 6: Origin of chiral induction in the enolate system.



The selectivity of attack increases with a decrease in temperature and an increase in the size of the electrophile. Experimentally, it is found that sodium enolates give a higher selectivity than the corresponding lithium enolates. The only drawback of this method is the limited number of electrophiles that react at a convenient rate at <0°C. The temperature restriction is due to the fact that Na and Li enolates tend to be unstable above 0°C.

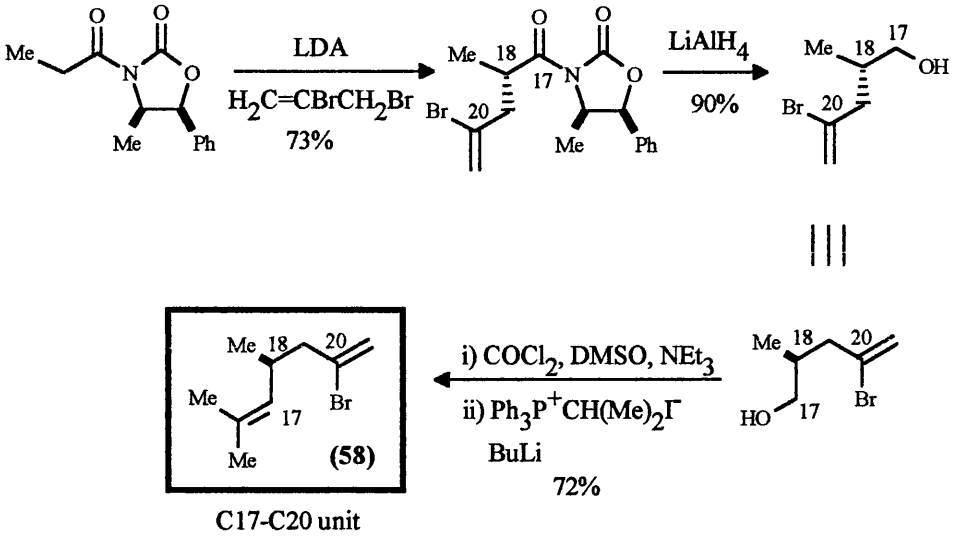
Nevertheless, this method has found application in natural product synthesis. For example, stereoselective alkylation was used to construct two units **(57)** and **(58)** used in a synthesis of the antibiotic X-206**[185]** (Scheme 19 and 20).

Scheme 19: Synthesis of the C3-C7 unit of the ionophore antibiotic X-206



C3-C7 unit **(57)**

Scheme 20: Synthesis of the C17-C20 unit of the ionophore antibiotic X-206



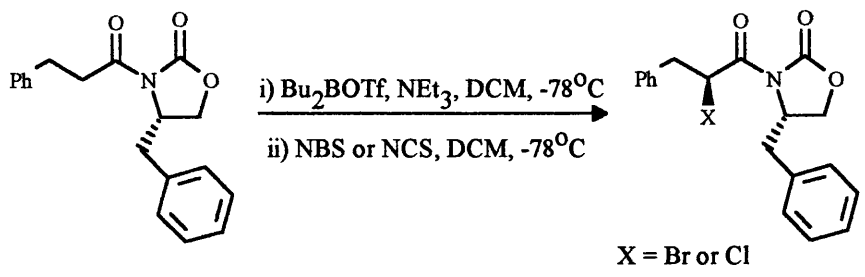
Apart from alkylation, enolates can be acylated**[186-7]** to give β-dicarbonyl substrates which are interesting compounds in themselves as the α-methene proton is not enolizable. This extra stability has allowed subsequent selective aldol reactions and nucleophilic additions to be carried out at the more electrophilic carbonyl group**[171,188-193]**.

2.5 : α-Substitution Reactions

2.5.1: α-Halogenations

Other heterocyclic C-X bond formations can occur with high selectivities. α-Halogenation using *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) have been shown to proceed in good yields**[194-6]** (Scheme 21).

Scheme 21

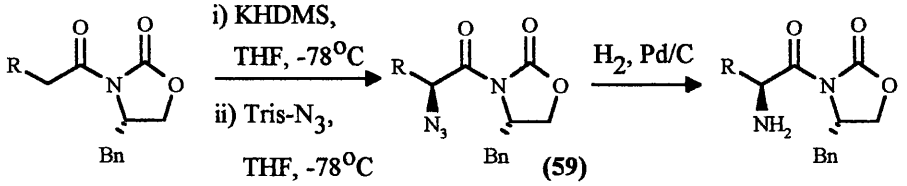


Bromination often occurs with a higher selectivity than chlorination primarily due to a greater steric demand. An increase in diastereoselectivity is also observed if triethylamine is replaced by diisopropylamine. α-Iodination is not possible, due to the instability of the α-iodocarboximides at room temperature. Reports have also shown that α-fluoro carboximides can be synthesised using fluorinating reagents**[197]** such as *N*-fluoro-*o*-benzenedisulphonimide (NFOBS), *N*-fluorobenzenesulphonimide and (+)-*N*-fluoro-2,10-camphorsultams.

2.5.2: α-Aminations

Amination can provide a direct entry into a wide range of valuable non-proteinogenic amino acids. There are three main methods of introducing an α-amino group into *N*-acyloxazolidinones. For example, in one procedure the treatment of an enolate directly with di-*tert*-butyl azodicarboxylate (DBAD)**[198,200]** gives an azide **(59)** (Scheme 22).

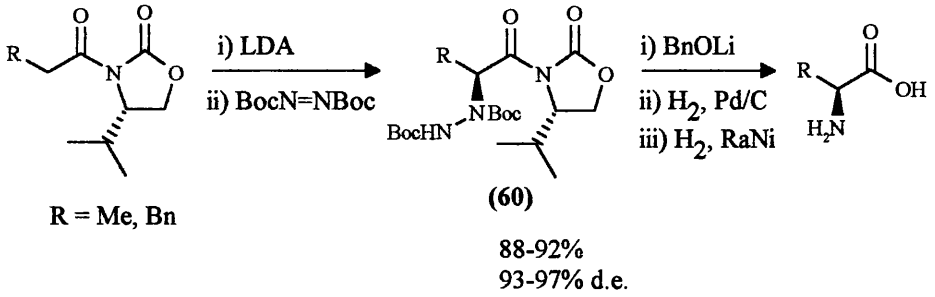
Scheme 22: α-Amination of *N*-acyloxazolidinones



R = Bn, Me, Ph, *t*-Bu, *i*-Pr, $CH_2CH{=}CH_2$ 71-91%
91-99% d.e.

Alternatively, the enolate can be treated with triisopropylbenzenesulphonyl azide (Tris-N_3)**[201]** to give a hydrazone derivative **(60)** (Scheme 23). Reduction**[202]** of these derivatives then furnished the aminated products.

Scheme 23

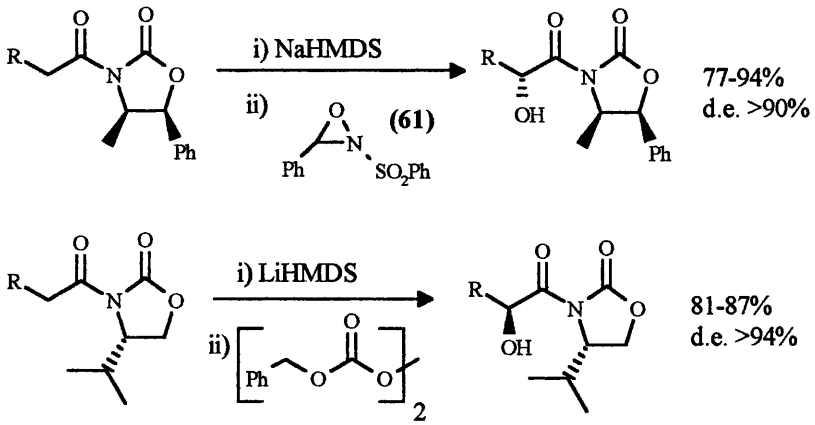


The third procedures may involve halogen displacement with tetramethylguanidium azide**[203-6]**. The product azides are then reduced to afford the desired α-amino carboximides.

2.5.3: α-Hydroxylations

α-Hydroxylated derivatives are best prepared by treating the sodium enolate of the appropriate *N*-acyloxazolidinones with an oxaziridine**[207] (61)**, or with dibenzyl peroxydicarbonate**[199]** (Scheme 24).

Scheme 24

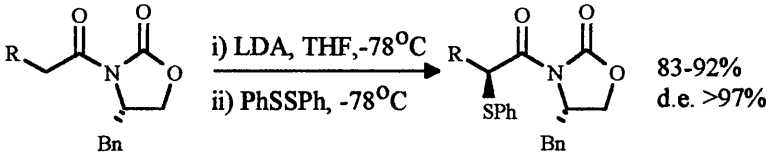


2.5.4: α-Sulphenylations

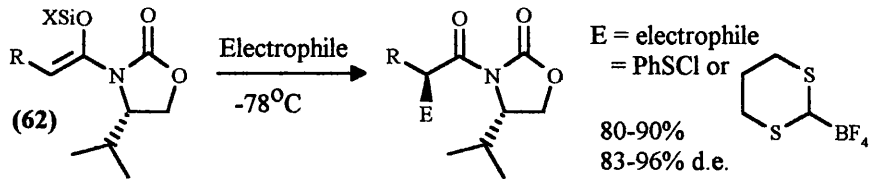
The sulphenylation of *N*-acyloxazolidinones can be accomplished in two ways. For example, high diastereoselectivity (>97%) was obtained by treating an appropriate

silyl enol ethers with phenyl disulphide**[208]**. On the other hand, the employment of silyl enol ethers**[209] (62)** in sulphenylation procedures have been reported. This involves the treatment of the silyl enol ethers with sulphenylating reagents such as thiophenyl chloride (PhSCl) or 1,3-dithieniuim fluoroborate. Activation of the silyl enol ethers by a Lewis acid is not required in these reactions (Scheme 25).

Scheme 25



R = *t*-Bu, *i*-Pr, *n*-Pr, Et

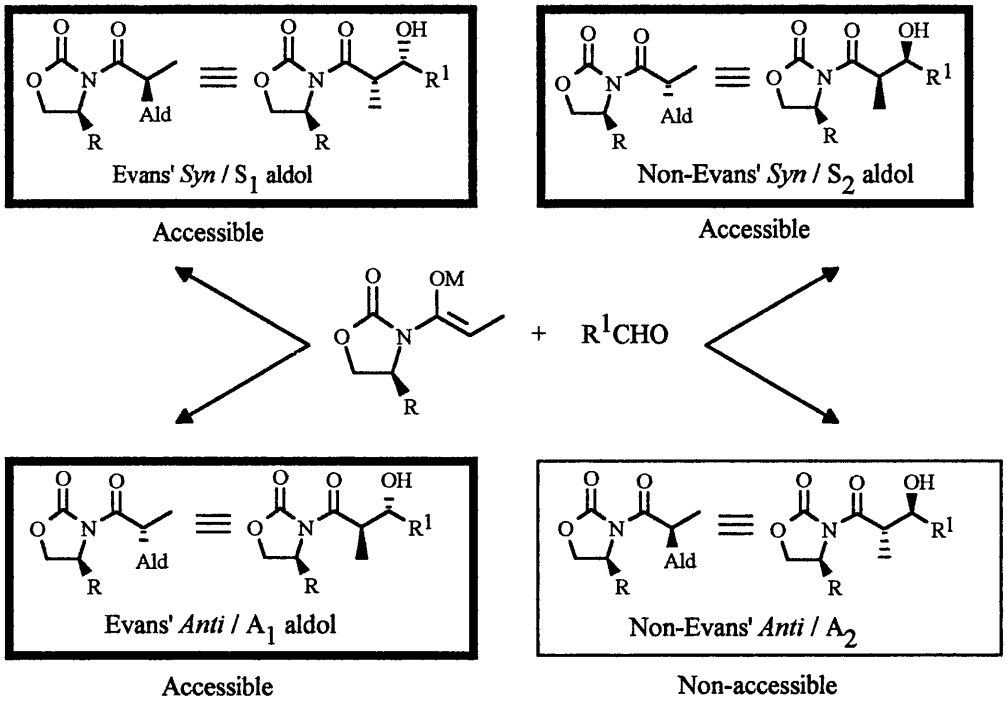


X = Me_3, Et_3, *t*-$BuMe_2$
R = Et, Me

2.6: Aldol Reactions

An important synthetic application of oxazolidinones lies in the area of aldolisation. Using the (*Z*)-enolate derived from *N*-acyloxazolidinones, it is possible to access three out of the four possible aldol adducts by careful choice of conditions (Scheme 26). In addition, these products are often obtained in high yields and diastereoselectivities. Boron and titanium enolates are usually used for aldol reactions as a high level of asymmetric induction is achieved.

Scheme 26



The opposite sense of induction is observed in aldol adducts compared to alkylated products. For an explanation, the aldol reaction between a boron enolate and an aldehyde can be considered. As a general observation **[168,183-4,196,210-2]**, a rigid boron chelated (*Z*)-enolate **(63)** is formed upon the treatment of *N*-acylated auxiliary with diisopropylethylamine (DIPEA) and dibutylboron triflate. This chelation is broken when an aldehyde is introduced into the mixture, as the oxygen atom of the aldehyde now associates with the boron atom. In this less rigid conformation **(64)**, the heterocyclic ring rotates through about 180° to lessen the repulsive dipole-dipole interaction between the two lone pair electrons of the oxygen atoms of the complex. In this arrangement **(65)**, the *i*-Pr group blocks the upper face of the enolate and directs the aldehyde to the lower face. The reaction then proceeds via the 'Zimmerman-Traxler' transition state, where the aldehyde and the enolate are held in a six-membered chair conformation **(66)**. In this transition state, the large R group of the aldehyde adopts an equatorial position to avoid adverse 1,3-diaxial interactions.

Similarly, the *i*-Pr group points away from the Bu group in this transition state. Thus, the Evans' *syn*-aldol products are obtained in excellent diastereomeric excess (Scheme 27).

Scheme 27

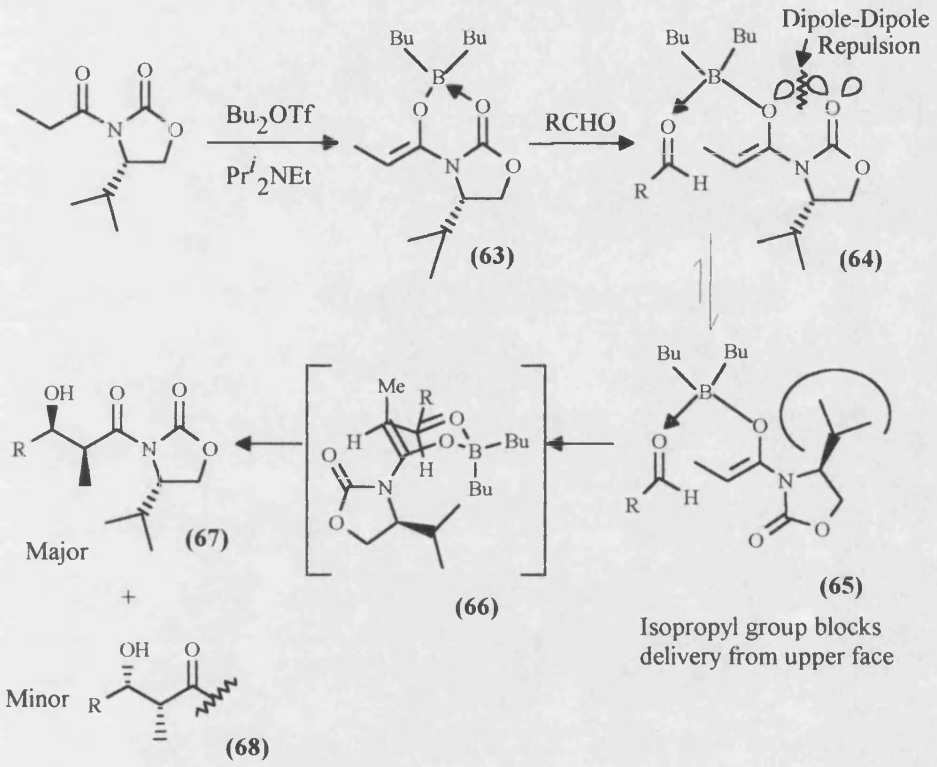


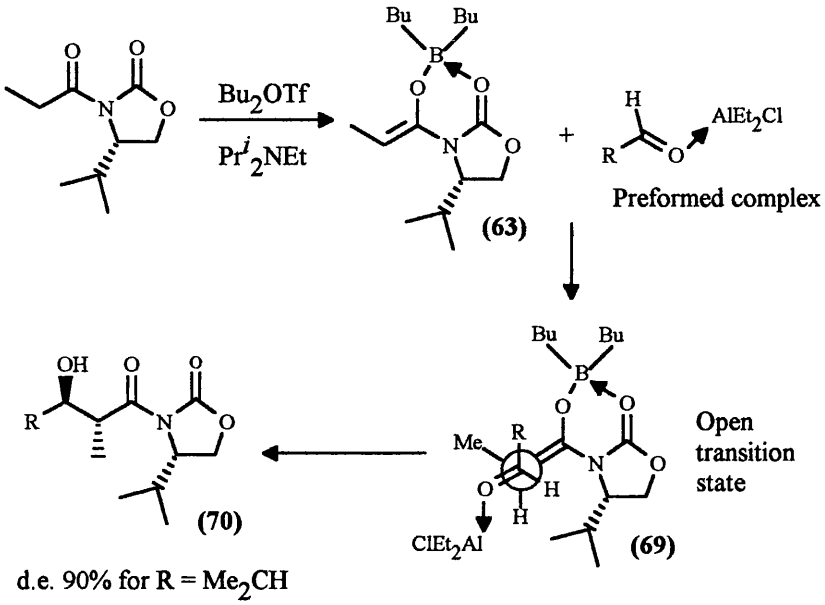
Table 6: Diastereomeric excess of aldol reactions

R group	ratio of 67:68
Ph	99.8:0.2
Bu^n	99.3:0.7
Pr^i	99.8:0.2

The formation of a non-Evans *syn* aldol product would require the attack of aldehyde from the other enolate face. This would lead to destabilizing interaction between the *i*-Pr and Bu groups. Therefore, this product is formed only as a minor component in the final mixture.

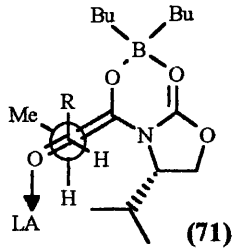
The use of an oxophilic element such as boron makes the transition state "tighter" due to the short B-O bond: B-O = 1.36-1.47, Å, Li-O = 1.92 Å, Al-O = 1.92 Å. However, the *anti*-aldol products can be obtained if the reaction is forced to proceed through an open transition state (Scheme 28).

Scheme 28



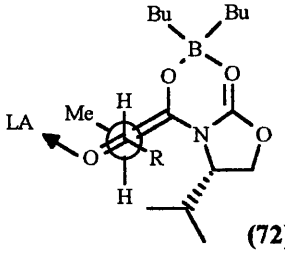
This is effective when an aldehyde-dimethylaluminum chloride (DMAC) complex**[213]** is used. This prevents the chelation of boron onto the aldehyde, allowing an open transition state **(69)**, from which *anti*-aldol products **(70)** are obtained. The use of excess Bu_2BOTf has a similar effect**[214]** and must be avoided if the desired product is the *syn* aldol adduct. A change in Lewis acid from the bulky Et_2AlCl to the smaller $TiCl_4$, or $SnCl_4$, also alters the product distribution to the non-Evans' *syn* aldol adducts. This can be explained by studying their transition states**[213]** (Figure 7).

Figure 7



(71)

Favoured by large Lewis acids
Anti-aldols



(72)

Favoured by small Lewis acids
Syn-aldols

When the interaction between the methyl vs R group in the gauche conformation is large relative to the Lewis acid vs methyl group, transition state **(72)** is favoured. The repulsive interaction is minimized in this conformation and it leads to non-Evans' *syn* aldol adducts. This only occurs if the size of Lewis acid is relatively small, however, the reverse is observed if the size of the Lewis acid is larger.

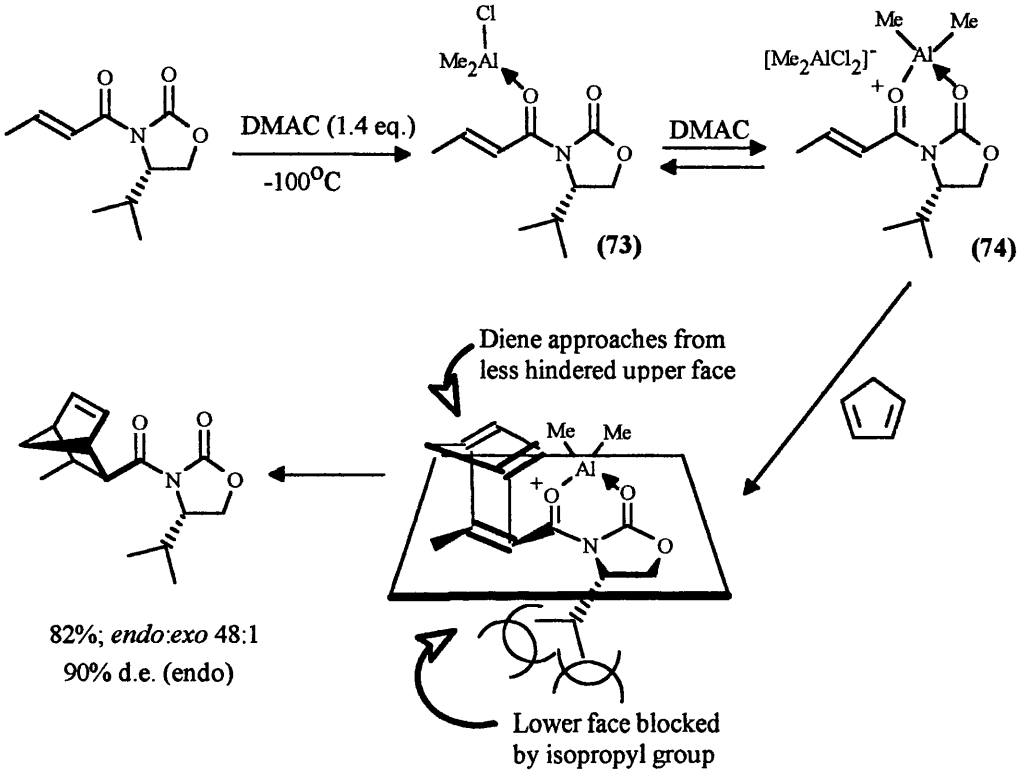
The use of the titanium enolate**[215]** in aldol reactions with aldehydes affords non-Evans' *syn* aldol adducts with high diastereofacial control. This is attributed to chelation control by the titanium enolate. Strong solvent effects**[216-7]** are reported to exist in these aldol reactions when a titanium enolate is used. A higher selectivity is observed when the solvent is changed from THF to diethyl ether, presumably due to its weaker binding affinity for the titanium enolate. The versatility of this method has found many synthetic applications in natural product synthesis**[170-1,218-222]**.

2.7: Diels-Alder Reactions

α,β-Unsaturated *N*-acyloxazolidinones undergo Diels-Alder reaction with dienes in the presence of dimethylaluminum chloride (DMAC)**[177]**. The *endo* products are obtained in high yield and diastereoselectivity. Chelation control again plays an

important part in asymmetric induction of such cycloadditions. The Diels-Alder reaction with cyclopentadiene is an example (Scheme 29).

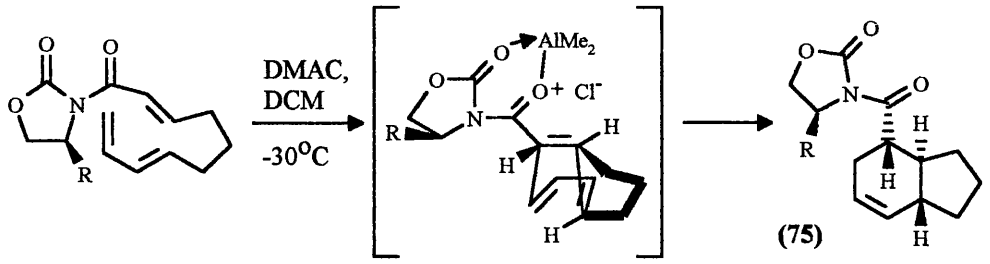
Scheme 29



In the reaction, the DMAC co-reagent initially forms an 1:1 complex **(73)** with the α,β-unsaturated *N*-acyloxazolidinone. However, if more than 1 equivalent of Lewis acid is added, a new positively charged complex **(74)** begins to form. This can be interpreted in terms of a reversible ionization of the complex as a result of its reaction with the excess Lewis acid. This ionised intermediate **(74)** is more reactive and conformationally more rigid. Under this arrangement, the cyclopentadiene is directed to the less hindered face, where at -100°C the steric effect is felt even more strongly. In addition, a higher selectivity is attained when the C4 position of oxazolidinone is phenyl substituted. The electronic repulsion between the aromatic ring and the diene results in an 'enhanced steric effect'**[223]**. Beside intermolecular

Diels-Alder reactions, the oxazolidinones are also used to control intramolecular Diels-Alder reactions[176, 224-5] where *endo* adducts **(75)** are synthesized in high diastereomeric excesses (Scheme 30).

Scheme 30



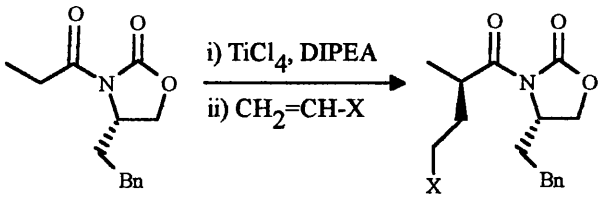
R	*endo*/*exo*
(*S*) *i*-Pr	92:8
(*S*) Bn	97:3

Such a reaction was used in the syntheses of the macrolide lepicidin[226] and pulo'upone [227].

2.8: Michael Addition Reactions[186,228]

The titanium enolates of *N*-acyloxazolidinones behave as nucleophiles and attack electron deficient alkenes in a highly diastereoselective manner (Scheme 31).

Scheme 31



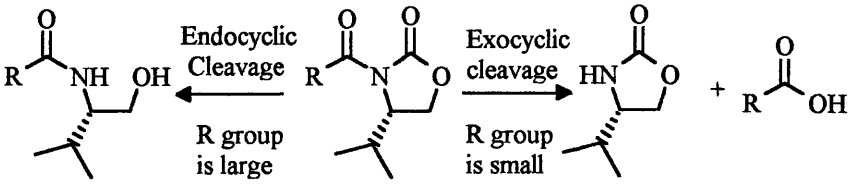
X = COEt	d.e.	>99:1
CN		98:2
CO_2Me		99:1
CO_2Bu-*t*		>95:5

The alternative conjugate additions of organocuprates[229,230] to α,β-unsaturated *N*-acyloxazolidinones have also been reported.

2.9: Recovery of Oxazolidinones

An outstanding feature of oxazolidinones is the ease with which the heterocycle is cleaved. This can be achieved without loss of stereointegrity where chiral oxazolidinones are concerned. Mechanistically, two processes are possible when *N*-acyloxazolidinones are involved, either ring-scission or *N*-deacylation (Scheme 32).

Scheme 32

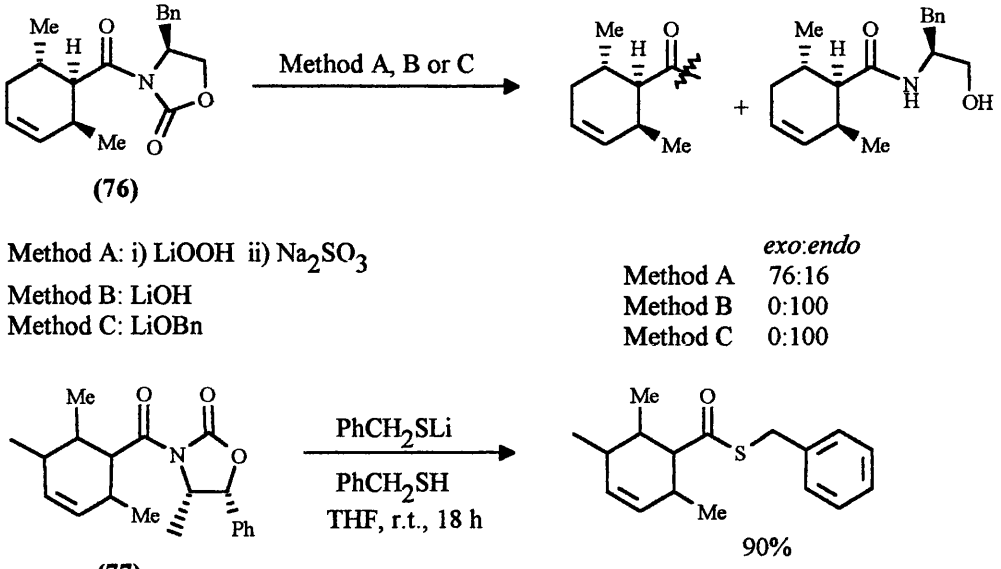


Normally, hydroxide ion will attack the exocyclic carbonyl group if the R group is not sterically demanding. This will lead to the recovery of both the appropriate acid RCO_2H and the parent oxazolidinone. However, if the *N*-acyl fragment is bulky, then the approach to the exocyclic carbonyl group is blocked. An endocyclic cleavage of the oxazolidinone occurs that leads to a *N*-acylated amino alcohol.

Specific reagents such as lithium peroxide**[177,231-2]**, benzyl mercaptan**[233]** and lithium benzylthiolate/ trimethylaluminum**[234]** have been used successfully in *N*-deacylations instead of the more usual reagent, lithium hydroxide. These reagents often give a better recovery rate of the parent oxazolidinones, especially where bulky *N*-acyloxazolidinones **(76)** and **(77)** are concerned (Scheme 33).

In addition, the employment of 'Quat' (5-substituted 3,3-dimethyl-2-pyrrolidinone**[235]**) or 'SuperQuat' (5,5-disubstituted 4-substituted oxazolidin-2-ones**[150-2]**) as auxiliaries will also favour exocyclic cleavage.

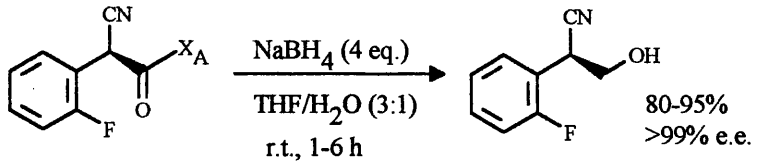
Scheme 33



The carboxylic acid group can be converted into other functional groups during cleavage. Such reactions can be broadly divided into four classes. For instance, *N*-acyloxazolidinones can be transesterified into methyl esters using magnesium methoxide **[207]**, into benzyl ester**[182,195,219,224-5,236-9]** and into thioester **[223,230,231,237]**. More recently, lanthanum(III) iodide/alcohol systems**[240]** have been used for transesterification. These reactions then occur with negligible racemization.

Reduction with lithium borohydride**[171,182,238,241-2]** and lithium aluminum hydride **[190-2,182,243-4]** leads to the formation of alcohols. Both of these reagents have limitations resulting from non-chemoselective reduction of other sensitive groups. In addition, the basic conditions generated may cause racemization. A reagent system using sodium borohydride**[245]** in 3:1 THF/water has been reported as an effective reductant in these cases and a range of racemization-prone substrates are cleaved with high yield and e.e. (Scheme 34).

Scheme 34



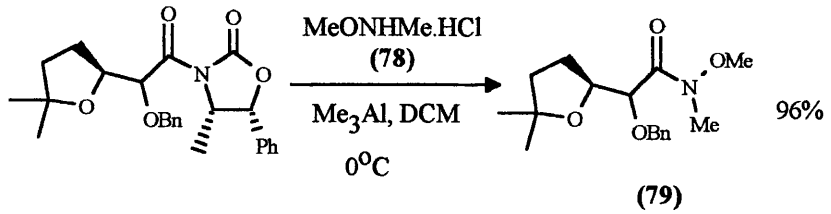
HX_A = oxazolidinones derived from phenylalaninol, valinol and ephedrine

The use of water as a co-solvent is found to be essential to suppress racemization, although its exact role in the process is uncertain.

Conversion of the *N*-acyl fragment to an aldehyde group can be achieved via reduction with diisobutylaluminum hydride (DIBAL)**[185]**. Alternatively, a two step approach **[190]** involving reduction/oxidation can be used.

If the desired products are amides, then metal-catalysed aminolysis**[246]**, or transamination with hydrazine**[247]** may effect the transformation. The *N*-acyloxazolidinones can also be converted into the synthetic versatile Weinreb amide **[185,248]** **(79)** with *N,O*-dimethylhydroxylamine hydrochloride**[249-251]** **(78)** (Scheme 35).

Scheme 35



(79)

This amide and its analogues may be converted to synthetically important aldehydes and ketones.

Summary I

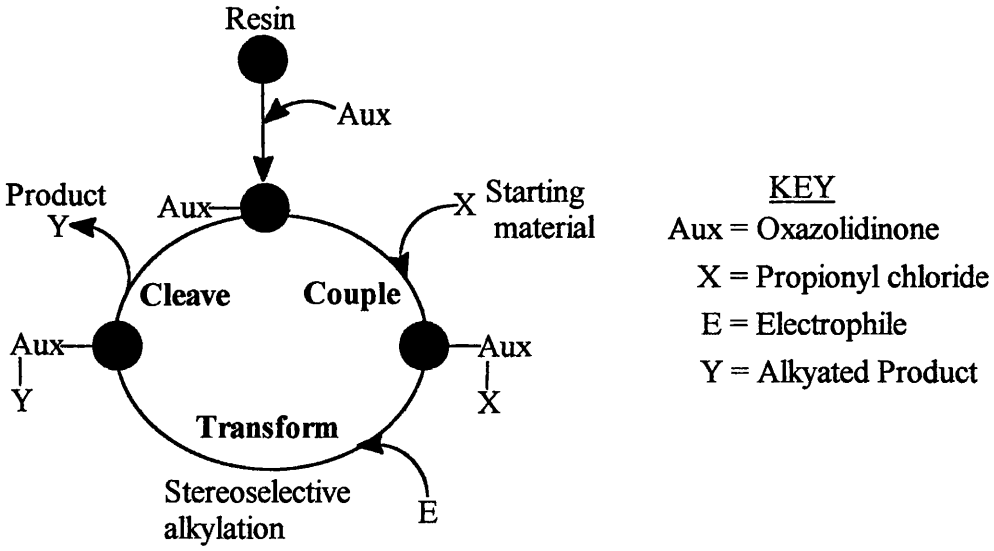
The synthetic utilities of oxazolidinones are enormous and cover a broad range of chemistry. The successful adaptation of these reactions to solid phase will be tremendously beneficial in synthetic methodology. However, we decided to concentrate our efforts primarily on the alkylation reactions of oxazolidin-2-ones as this seemed to provide a very useful entry into compounds needed in pharmaceutical industry. Thus, the research proposed for this Ph.D. programme can be summarised as follows: *the synthesis of a recyclable resin-bound oxazolidinone and an investigation into its efficacy in solid phase asymmetric alkylations.*

3: Results and Discussions

3.1: Research Proposal

The object of this research was the synthesis of a resin-bound chiral oxazolidin-2-one. Upon *N*-acylation, the acyl fragment could be enolised with a lithium alkyl to form a chelated imide enolate. The presence of a chiral centre in the auxiliary should render two faces of the enolate diastereotopic, and interaction with suitable electrophiles would furnish the derivatives with transfer of chirality at the α-position. After hydrolysis, the auxiliary could be released and a library of useful optically pure acids would result. A cyclic system utilising the auxiliary can thus be envisaged (see Figure 8).

Figure 8: Summary of research proposal

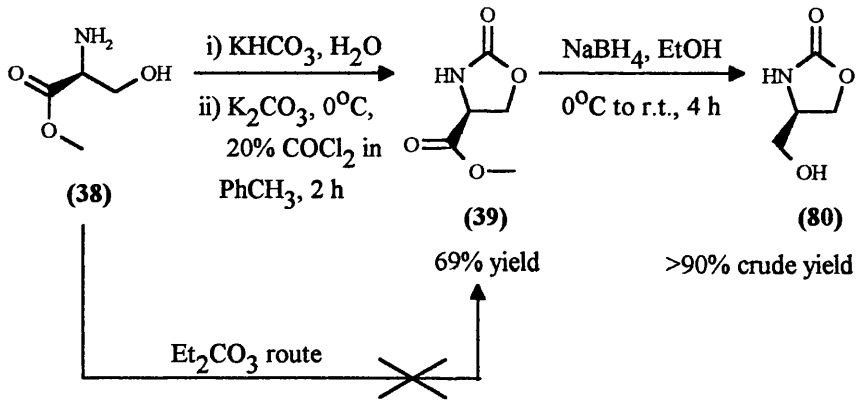


3.2: Synthesis of oxazolidinones derived from (*S*)-serine methyl ester

A primary requirement of the oxazolidin-2-one auxiliary is the presence of a substituent capable of coupling to a resin. This led us to the initial choice of a hydroxymethyl group for which the methyl ester of (*S*)-serine was selected as the starting material. Cyclisation to the heterocycle **(80)**, where this group is appended

to the C-4, can be achieved with phosgene[125,149,168] or diethyl carbonate[130]. Both were evaluated by us as a source of the intramolecular carbonyl function. In the event, phosgene proved to be more useful giving a moderate yield of the ester (69%) after distillation. Eventually, this product formed as an amorphous solid, a fact which did not facilitate purification. The methyl ester group of this product **(39)** was reduced successfully with sodium borohydride in ethanol to afford the required alcohol **(80)** in >90% yield (Scheme 36). Its purity and authenticity was checked by spectroscopy and by comparison with physical data quoted in the literature[149].

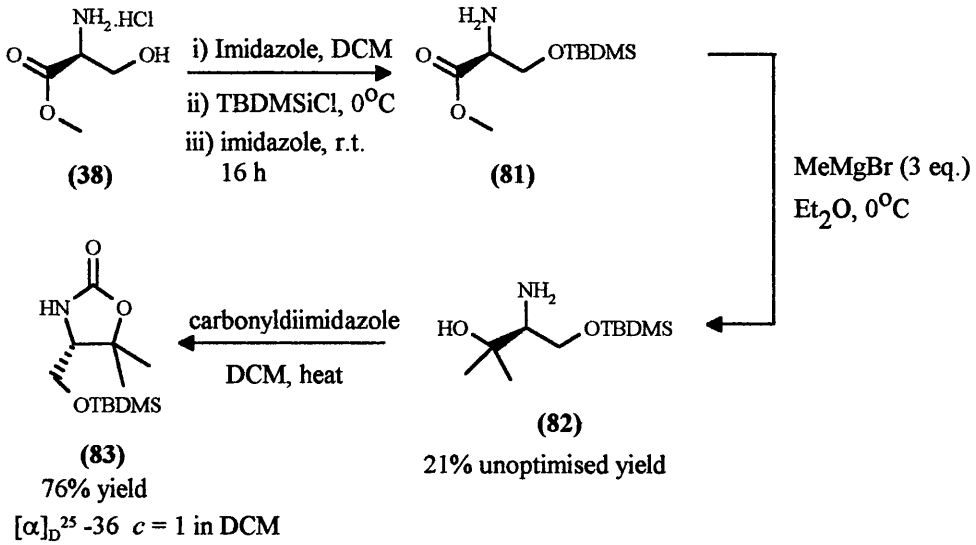
Scheme 36: Synthesis of (*R*)-4-hydroxymethyloxazolidin-2-one **(80)**



At this stage of synthesis, we became aware that 5,5-dimethyloxazolidin-2-ones[150-2] tend to be crystalline solids, so we switched our attention to the *gem*-dimethyl analogue protected as the ^{t}butyldimethylsilyl ether **(83)** [252]. In this route, a key step is the reaction of the silylated ester with excess methylmagnesium bromide in diethyl ether at 0°C (Scheme 37). In our hands this afforded the tertiary alcohol **(82)** in a 21% unoptimized yield compared to a literature yield of 41%[152]. We noted however that the intermediate ketone is present in the reaction mixture and clearly further reaction with methyl magnesium bromide should raise this yield somewhat. Next we reacted this product with carbonyldiimidazole in DCM at 40°C to afford the

target compound **(83)** in 96% yield (76% after purification of the crude reaction product) (Scheme 37).

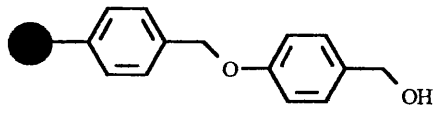
Scheme 37: The synthesis of oxazolidinone **(83)**



3.3: Model study into solid phase coupling method

This seemed a reasonable beginning but, before proceeding, we now gave some further thought about the best substituent group to facilitate coupling to the resin. The resin we decided to use was a Wang**[253]** type, the terminus of which is a 4-hydroxymethylphenyloxy unit (Figure 9).

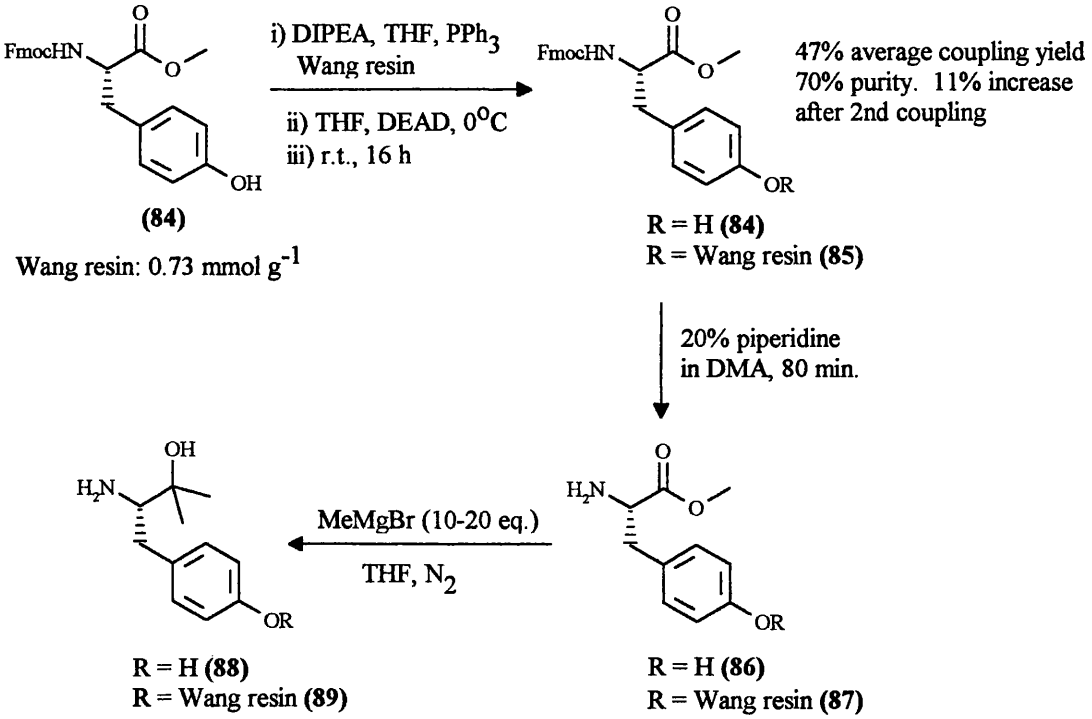
Figure 9: Structure of Wang resin



Coupling thus generates an ether link and for this the Mitsunobu reaction**[254-6]** is most suited via a phenol. Some successful results **[257-260]** have been achieved with a range phenolic compounds bonded through a 4-hydroxybenzyl substituent and this indicated to us that tyrosine, rather than serine, should be a better starting material for the auxiliary. This would also increase the steric bulk at the C-4

position. The latter being useful in enhancing diastereoselective control. To test the coupling efficiency in a model experiment, we synthesized *N*-Fmoc protected methyl tyrosine ester **(84)** and reacted it with Wang resin under Mitsunobu conditions. Diisopropylethylamine**[258]** (DIPEA) was used instead of *N*-methylmorpholine**[257]** (NMP) as this base gave a cleaner coupling reaction. An average coupling yield of 47% was obtained over two attempts, but this could be increased by 11% if the Mitsunobu procedure was repeated on the initial product [yield based on uncapped resin only] (Scheme 38).

Scheme 38: Mitsunobu coupling of Fmoc-Tyr-OMe **(84)** onto Wang resin



It occurred to us that, with this amino acid ester appended to the resin, we might complete the synthesis of the 5,5-dimethyloxazilidin-2-one on the support. Thus, the resin bound *N*-protected tyrosinate **(85)** was treated with benzoyl chloride to cap unreacted alcoholic sites. The Fmoc protecting group was removed using 20% piperidine in dimethylacetamide (DMA) to afford the supported amino ester **(87)** (R

= resin). This compound was then treated with methyl magnesium bromide in THF at 0°C for four hours. Before proceeding to the cyclisation step, we decided to investigate the nature of the product. So after workup, the crude mixture was cleaved from the resin with 95% trifluoroacetic (TFA) acid and the product was analysed by reverse phase HPLC. Eleven components were shown to be present (Table 7).

Table 7: Retention time and area percentage of reaction mixture

	Retention time (in minute)	Area %		Retention time (in minute)	Area %
Peak 1	3.49	45.8	Peak 7	11.4	1.67
Peak 2	6.01	32.4	Peak 8	13.4	0.26
Peak 3	6.70	3.88	Peak 9	19.0	0.32
Peak 4	7.11	8.77	Peak 10	21.5	1.95
Peak 5	8.58	0.86	Peak 11	25.3	0.58
Peak 6	8.90	3.50			

Analysed using a Phernomex Spherisorb 5μm ODS2 column eluted in 1 ml min^{-1} with CH_3CN/0.1% TFA in water

It was a reasonable conclusion that the more abundant products 1 and 2 were the alcohol **(88)** (R = H) and the unreacted ester **(86)** (R = H) (see Scheme 38). Three further Grignard reactions were carried out with the substrate bound to the resin under various conditions and, after cleavage from the resin, the crude reaction products were evaluated by HPLC. The results are summarised in the Table 8.

Table 8: HPLC analysis of solid phase Grignard reactions

	Reaction conditions	Retention time		% area	
		Peak 1	Peak 2	Peak 1	Peak 2
run 1.*a*	MeMgBr (10eq), 4 h, 0°C	3.49	6.01	45.7	32.4
run 2.*a*	MeMgBr (10eq), 6 h, 0°C	2.69	6.30	68.4	25.1
run 3.*b*	MeMgBr (10eq), 22 h, 0°C	3.47	6.75	65	25.2
run 4.*b*	MeMgBr (20eq), 72 h, 0°C then r.t. for 2 d before heating at 60°C for 2 h	3.27	6.66	74	11.6

a) Analysed using a Phernomex Spherisorb 5μm ODS2 column eluted in 1 ml min^{-1} with CH_3CN/0.1% TFA in water. b) Analysed using a PhaseSep Nucleosil 5μm ODS2 column eluted in 1 ml min^{-1} with CH_3CN/0.1% TFA in water

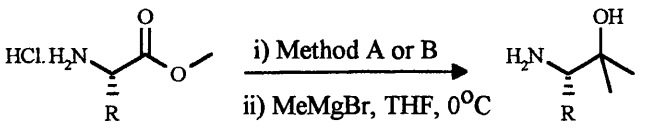
The HPLC traces all showed two main peaks, one of which increased as the reaction time and severity increased and another, which decreased. Although we could prove the latter was due to starting material **(86)**, the analysis of the other component or product was unsatisfactory. This problem was exacerbated by the fact that after cleavage from the resin, the starting material **(86)** and product **(88)** (R = H) had the same relative mass of 195. Of course, we could have solved the identity of the product by an independent synthesis and a comparison of retention data, however, the slowness of the reaction on resin persuaded us that a better approach would be to prepare (4*S*)-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(90)** directly and to couple it later.

3.4: Synthesis of oxazolidinones derived from (*S*)-tyrosine derivatives

3.4.1: Synthesis of 5,5-dimethyl-4-substituted oxazolidinone

For this, we decided to follow the conditions used by Davies**[150]** in his synthesis of methylated oxazolidin-2-ones as shown below. Thus, commercially available tyrosinate hydrochloride was desalted before treating with 3 equivalents of methyl magnesium bromide (Scheme 39).

Scheme 39



(91)

3-49% yield

R = $CH_2C_6H_4OBn$

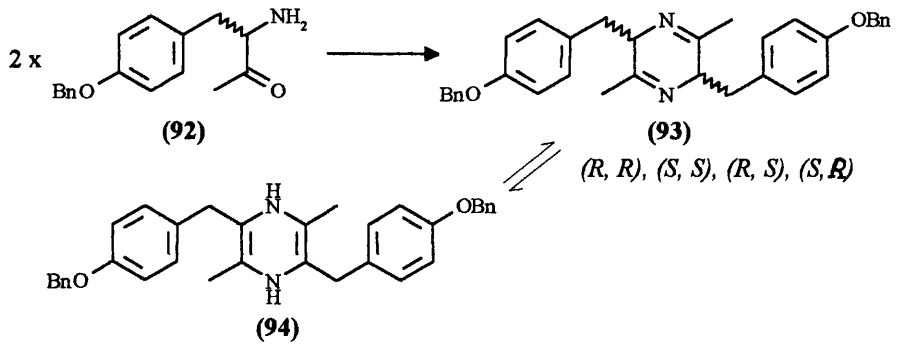
Method A: 33% $MeNH_2$ in EtOH

Method B: Na_2CO_3, DCM

Disappointingly, only 3-49% of the dimethyl alcohol **(91)** was obtained after chromatography. The problem is the presence of a free amino group, which

consumes one equivalent of the Grignard reagent. Thus, the resultant anion inhibits further reaction. There is some inconclusive evidence, however, that the amino ketone **(92)** may have formed. Thus, the reaction produced a crude product, which in its crude ^{1}H NMR spectrum clearly shows the AMX spin-spin system associated with the methylene-methine resonances. It would be anticipated that were the ketone to be present, its acetyl methyl protons would resonate as a 3H singlet at ~2.1-2.5 ppm. The spectrum, however, shows <u>two</u> singlets close together at ~2.8 ppm with an overall integral height corresponding to 3H. There is no clearly defined NH_2 resonance, although a NH proton resonance could be present at ~7.3 ppm. Indeed the IR spectrum, recorded in the same solvent ($CDCl_3$), exhibits a broad band at ~3386 cm^{-1}. Interestingly, there is a band at ~1661 cm^{-1} , which is more in keeping with an imine C=N stretching frequency than with that of a simple ketone. This is also the case with the ^{13}C NMR low field resonance which occurs at 175 ppm. Typically, a methyl ketone resonates at 200-210 ppm. It is conceivable that the amino ketone gives rise to a diastereomeric mixture of piperazines **(93)**. Racemisation could occur before or after cyclisation. Furthermore, the piperazines could be in tautomerism with the 1,4-diazine isomer **(94)** (Scheme 40).

Scheme 40

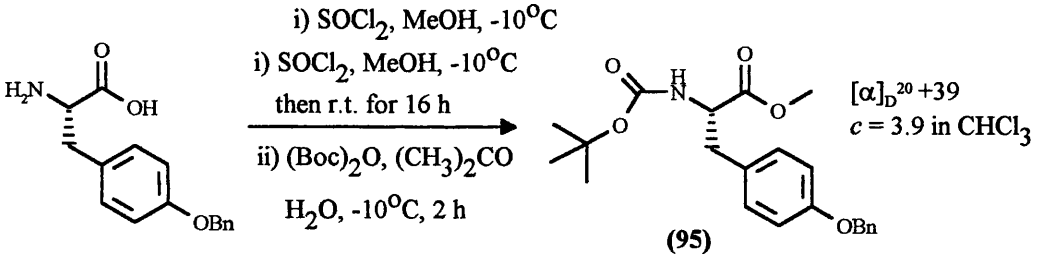


Thus, one possibility is if the piperazines **(93)** are the dominant tautomer in the reaction product, the resonances of the methyl group in the diastereomers may conceivably be at different chemical shift.

Disappointing, the mass spectrum of the crude product does not show a molecular ion species in +ES, EI, CI, +FAB modes which accords with either the amino ketone, piperazine or their tautomer. Instead there are two peaks in the +FAB spectrum, for example at m/z 268 and m/z 286. The ketone **(92)** would require $(M+1)^+$ at m/z 269 and the piperazine at m/z 503. Whatever the true nature of the product(s) from this reaction, we could not improve upon the maximum yield for the formation of the alcohol **(91)** and so we decided to protect the amino group of the starting material *via* the *N*-^{t}butyloxycarbonyl (Boc) derivative.

The synthesis then proceeded as follows. Firstly, (*S*)-*O*-benzyltyrosine was esterified with thionyl chloride in methanol to give the methyl (*S*)-*O*-benzyltyrosinate. This was protected as the *N*-Boc derivative **(95)** in 89% yield (Scheme 41).

Scheme 41

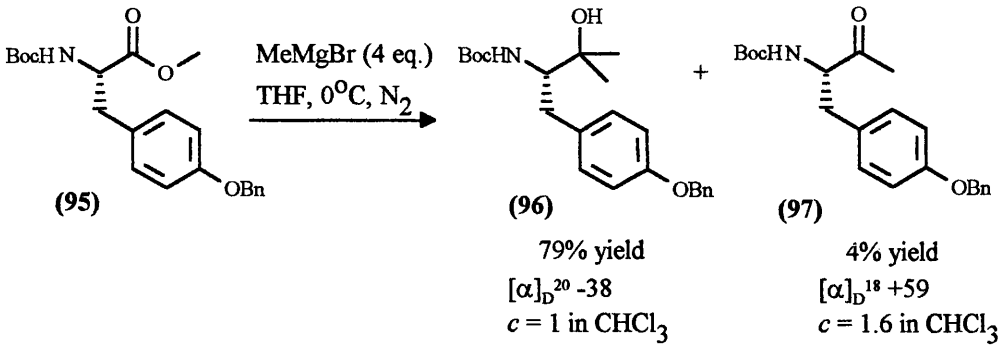


(95)

89% yield

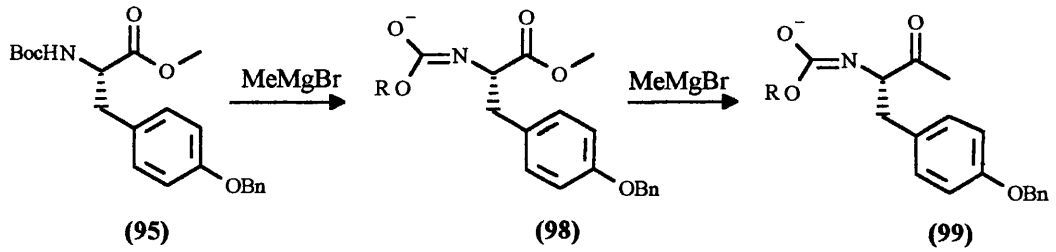
Subsequent treatment with four equivalents of methyl magnesium bromide afforded the *gem*-dimethyl alcohol **(96)** in 79% with $[\alpha]_D^{20}$ -38 c = 1 in $CHCl_3$. The ketone **(97)** was also obtained in 4% yield with $[\alpha]_D^{18}$ +59 c = 1.6 in $CHCl_3$ (Scheme 42).

Scheme 42



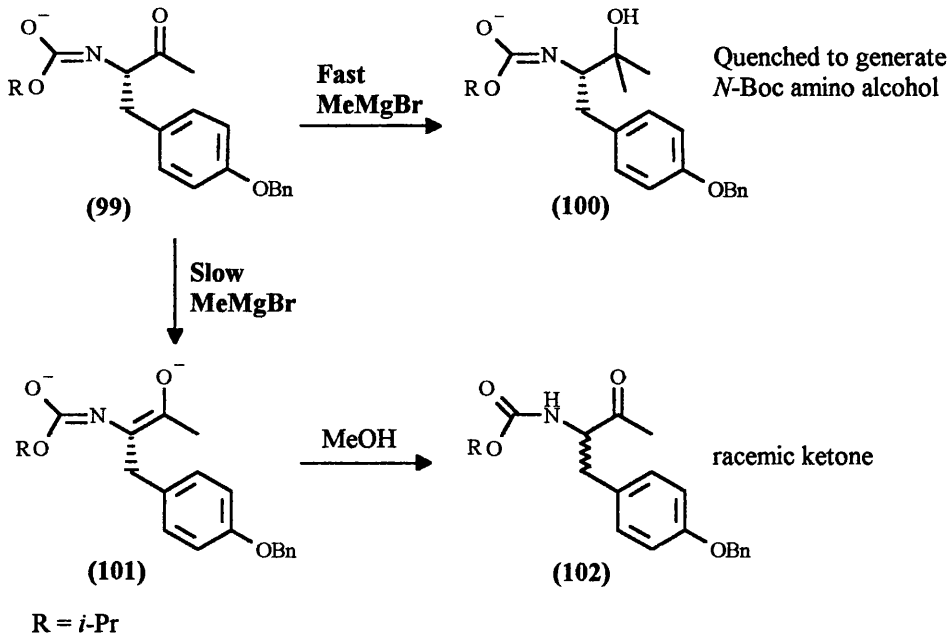
An increase in reaction time from 16 h to 34 h induces racemisation of these *N*-Boc amino ketones**[151]**. The racemization may well occur as follows: two equivalents of Grignard reagent are consumed to form the ketone species **(99)** (Scheme 43).

Scheme 43: Proposed mechanism of racemization



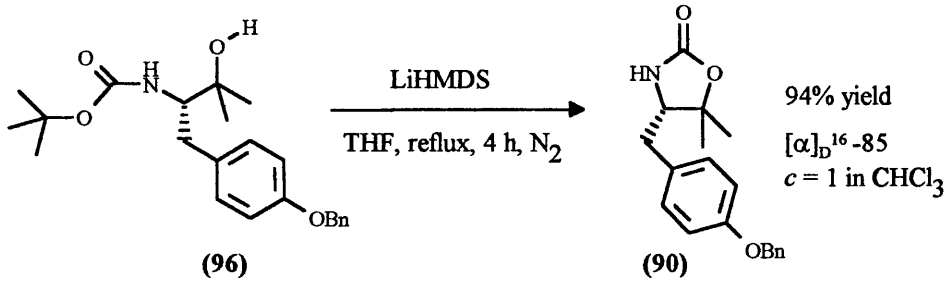
This species **(99)** can be attacked in two ways; a nucleophilic addition of the third Grignard reagent to the ketone yields the alcohol **(100)** and this constitutes the major reaction pathway. The minor pathway involves dianion formation and enolisation at the chiral centre. The process has to be irreversible, since reversibility would lead to the formation of the oxazolidin-2-one as a racemic compound. It is likely that the dianionic nature of the magnesium enolate **(101)** prevents further attack by the Grignard reagent and only forms the racemic ketone **(102)** upon quenching (Scheme 44).

Scheme 44



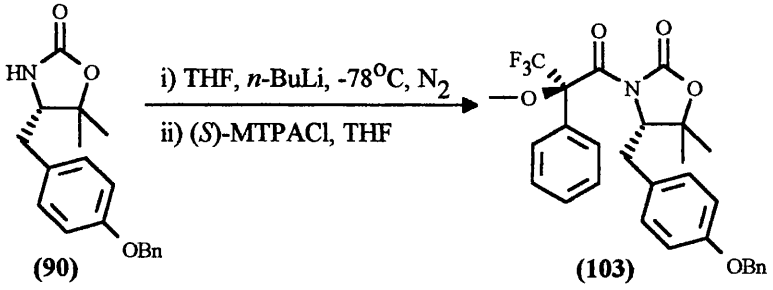
Cyclization to the optically pure 5,5-dimethyloxazolidin-2-one **(90)** was effected by the reaction of the alcohol **(96)** with lithium bis(trimethylsilyl)amide (Scheme 45).

Scheme 45



This gives a highly crystalline product in 94% yield with $[\alpha]_D^{16}$ -85 c = 1 in $CHCl_3$, which can be recrystallized from either methanol or ethanol. Its enantiomeric purity was assessed by ^1H NMR spectral analysis of the Mosher amide derivative**[261-3]** (Scheme 46).

Scheme 46: Formation of Mosher amide derivative

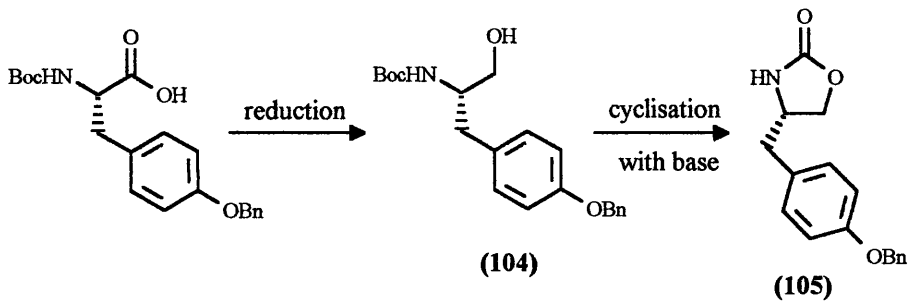


The auxiliary **(90)** was deprotonated with *n*-butyl lithium and *N*-acylated with (*S*)-methoxytrifluoromethylphenylacetic acid chloride. The crude product **(103)** was submitted to NMR analysis without any further purification. The 270 MHz ^{1}H NMR spectrum did not show any signals from the other potential diastereomer, although signals due to Mosher's acid and starting material were noted. Confirmation of the chiral purity of the auxiliary is discussed in a later section.

3.4.2: Synthesis of 4-substituted oxazolidinone

In parallel with this work, we also synthesized the unmethylated oxazolidin-2-one **(105)**, so that we might compare the stereoselectivity offered by the two auxiliaries once they are bonded to the resin. The synthesis mirrored much the same pathway as previously, using (*S*)-*N*-Boc-*O*-benzyltyrosine as the starting material (Scheme 47).

Scheme 47: Outline of synthetic route to 4-substituted oxazolidinone



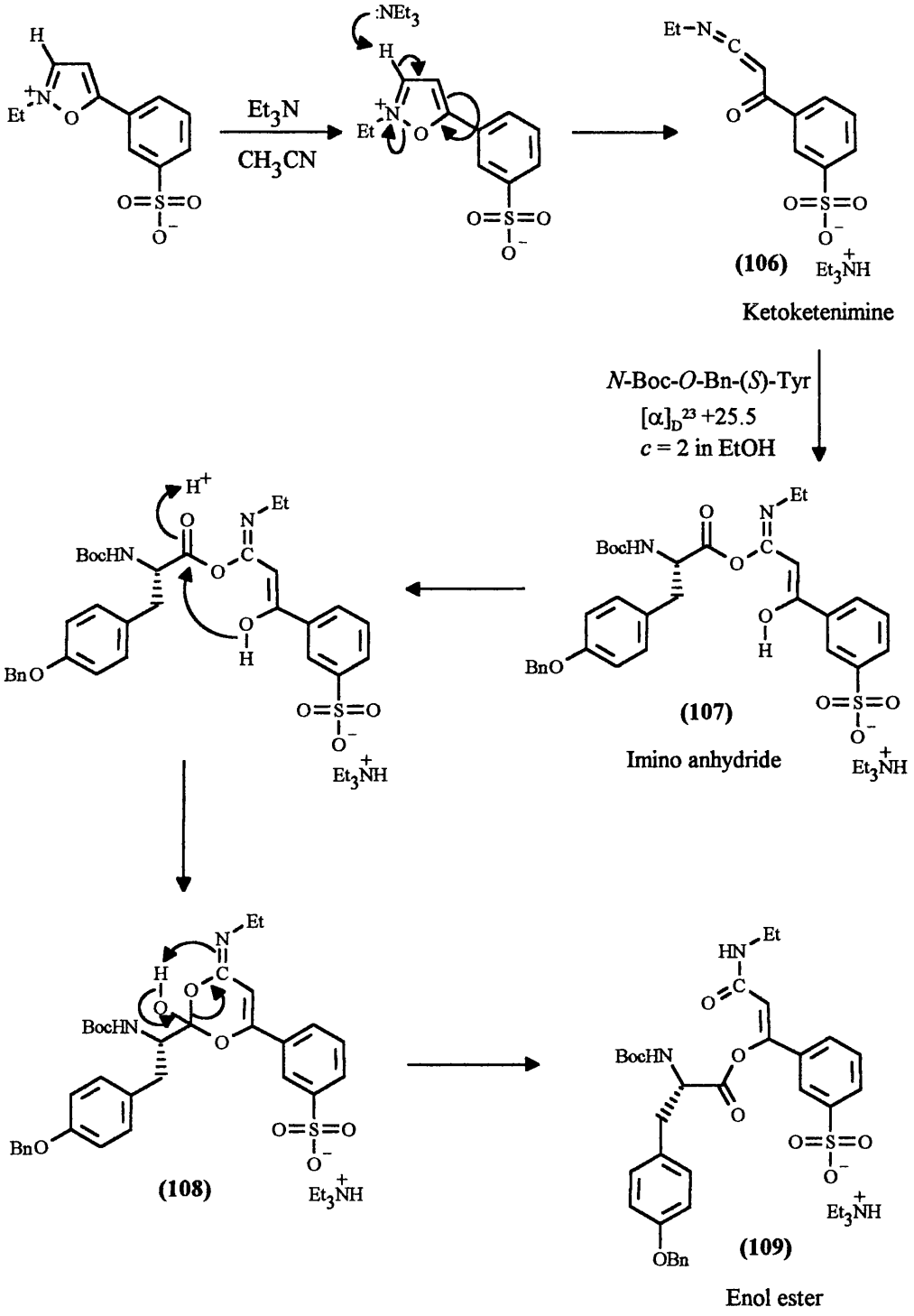
Cyclisation of the oxazolidin-2-one **(105)** occurred when the alcohol **(104)** was treated with lithium bis(trimethylsilyl)amide.

It should be noted, however, that the carboxylic acid of the starting material cannot be reduced using lithium aluminum hydride. This would cleave the Boc group**[264]**, and as a result a more selective method was sought. The weaker reductant sodium borohydride had been used for reactions with acids, but often requires an activating agent and harsh conditions**[265-7]**.

An indirect approach involved the reduction of the alkyl esters**[268-9]**or more attractively, activated esters**[270]** that can be formed *in situ* and reduced under mild conditions. For our purposes racemisation has to be avoided so mild conditions were mandatory.

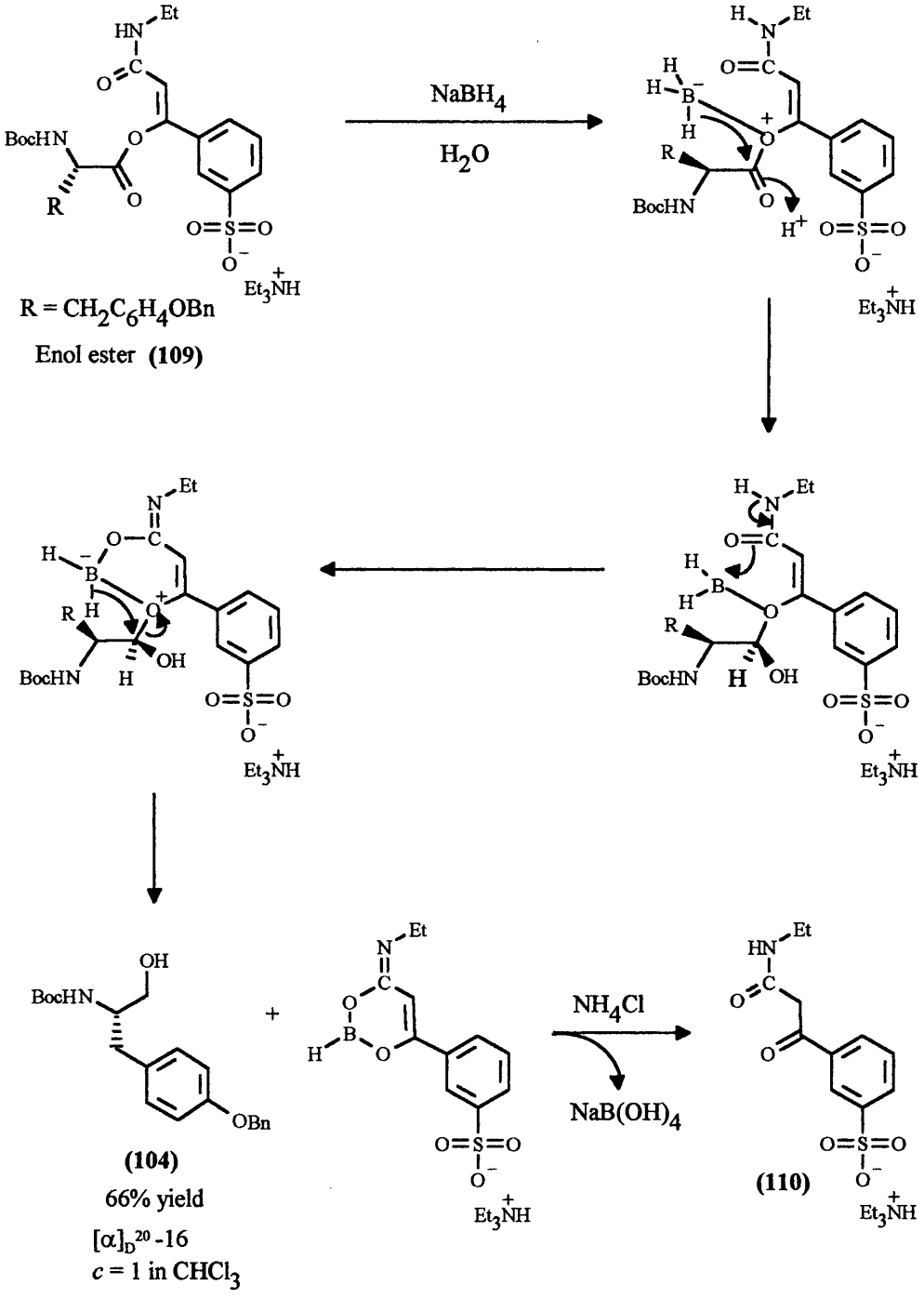
In order to achieve this, *N*-ethyl-5-phenylisoxazolium-3'-sulphonate (NEPIS)**[271-4]** was used. It is activated by the co-reagent triethylamine in the first step of the procedure, this decyclises the reagent to give the highly reactive ketoketenimine **(106)**. This ketoketenimine **(106)** then combines quickly with the carboxylate group of the tyrosine to generate an imino anhydride **(107)**. Although this intermediate cannot be detected directly, indirect experimental evidence exits for its formation**[272]** and it rapidly undergoes an acyl shift, similar to that of acyl salicylamides**[275]**. The end product is an enol ester **(109)**, which activates the carboxylate group to attack by sodium borohydride (Scheme 48).

Scheme 48: The conversion of ketoketeneimine **(106)** to imino anhydride **(107)**



The manner of the reduction is unsubstantiated but may utilise chelated boranes. In any event we obtained the required pure alcohol **(104)** in 66% yield and $[\alpha]_D^{20}$ -16 *c* = 1 in $CHCl_3$ (literature**[276]** $[\alpha]_D^{18}$ -17 *c* = 6 in $CHCl_3$) (Scheme 49).

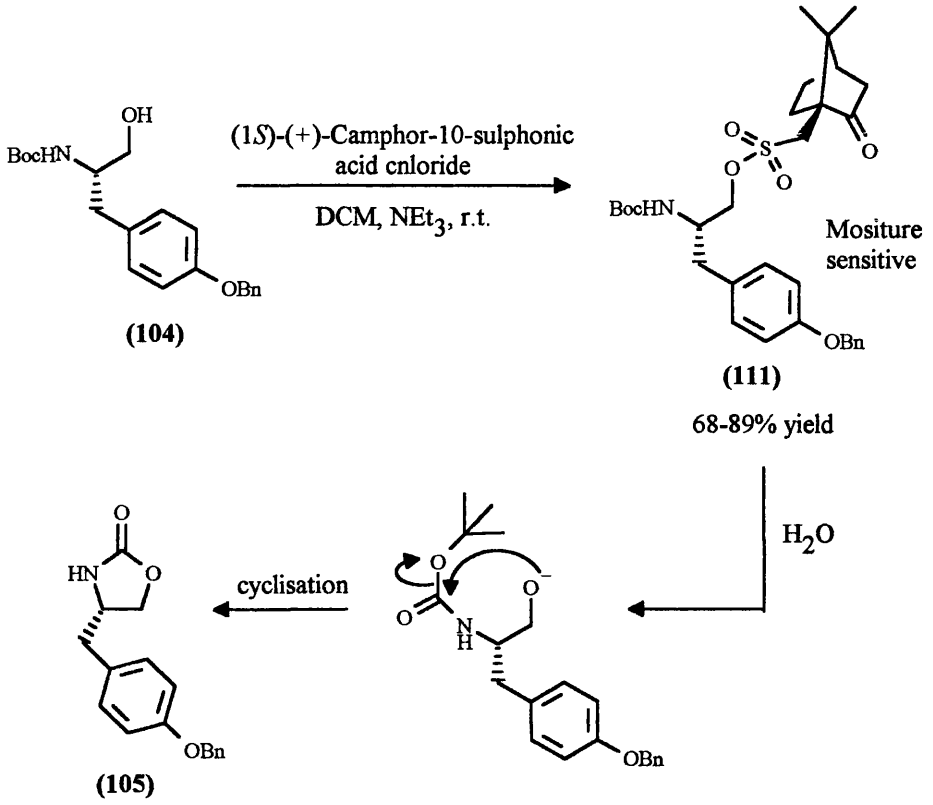
Scheme 49: The reduction of an enol ester **(109)** with $NaBH_4$



Chemical derivatization with (*1S*)-(+)-camphor-10-sulphonyl chloride[277] afforded the sulphonate **(111)** in yields ranging from 68% to 78%. Analysis of its 270 MHz ^{1}H NMR spectrum failed to detect the other diastereoisomer. The compound must

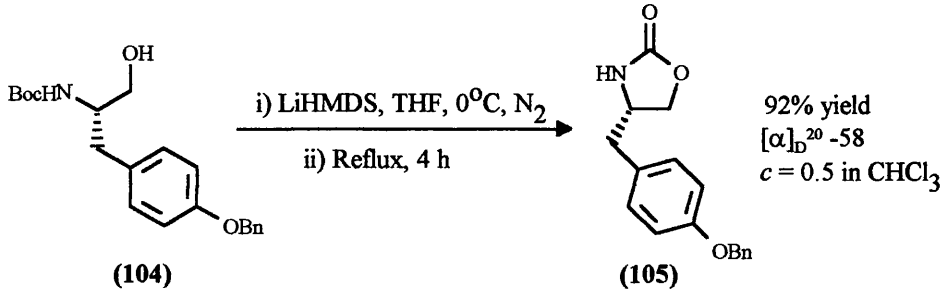
be stored under anhydrous conditions since it is easily hydrolysed and then cyclizes to the oxazolidin-2-one **(105)** (Scheme 50).

Scheme 50: Formation of chiral sulphonate **(111)**



Treatment of the amino alcohol **(104)** with lithium hexamethyldisilane (LiHMDS) afforded the target oxazolidin-2-one **(105)** in 92% $[\alpha]_D^{20}$ -58 (literature**[278]**: $[\alpha]_D^{18}$ -84.8 $c = 0.5$ in $CDCl_3$) (Scheme 51).

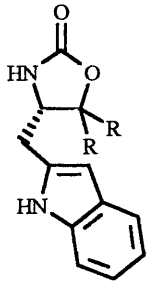
Scheme 51: Cyclization of *N*-Boc amino alcohol **(104)** to oxazolidin-2-one **(105)**



We note that other suitable oxazolidin-2-ones such as **(112)** and **(113)** are now recommended as potential auxiliaries (Figure 10), but although these may offer

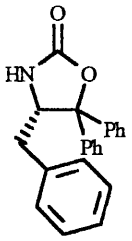
advantages in certain applications, we considered that we should now evaluate the compounds we had rather than include them.

Figure 10: Other oxazolidin-2-ones of interest



Cardillo *et. al.*
Tetrahedron Asymmetry
1995, **6**, 1947
R = Me, *n*-Pr, *n*-Bu

(110)



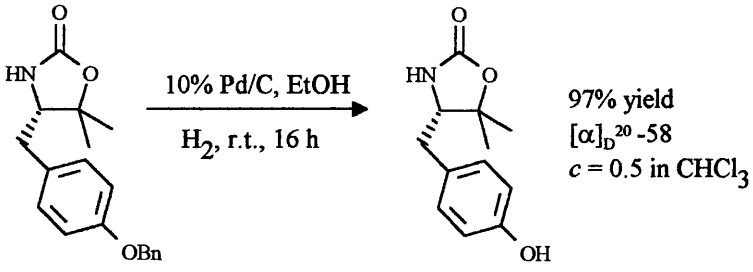
Isobe and Fukuda
Japanese Patent
JP09143173, 1995
Chem. Abstr., 1997
127, 50635

(111)

3.5: Solid Phase Synthesis of Resin-Bound Oxazolidinone

The coupling of 5,5-dimethyloxazolidin-2-one **(90)** onto the Wang resin could now proceed with a sufficient quantity of the material in hand. However, the auxiliary must be *O*-deprotected first to reveal the phenolic group, which is used as a handle of attachment. Debenzylation was carried out by catalytic hydrogenation**[279]** to afford the free phenolic compound **(114)** in over 97% yield (Scheme 52).

Scheme 52

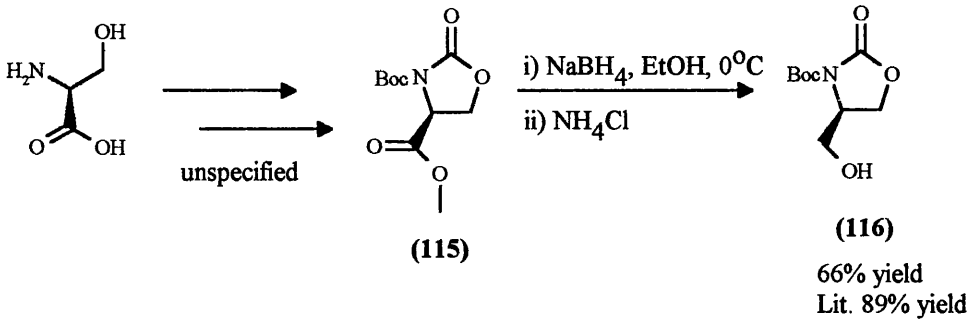


(90) **(114)**

At the time of this work, a report by Allin and Shuttleworth**[280]** on the syntheses of chiral carboxylic acids using a resin-bound Evans auxiliary was released. The 4-substituted auxiliary **(116)** used was derived from (*S*)-serine and the key step was the

sodium borohydride reduction of the ester **(115)** to give the alcohol **(116)** in a moderate yield of 66% (Scheme 53).

Scheme 53: Allin and Shuttleworth route to oxazolidin-2-one **(116)**



(115)

(116)

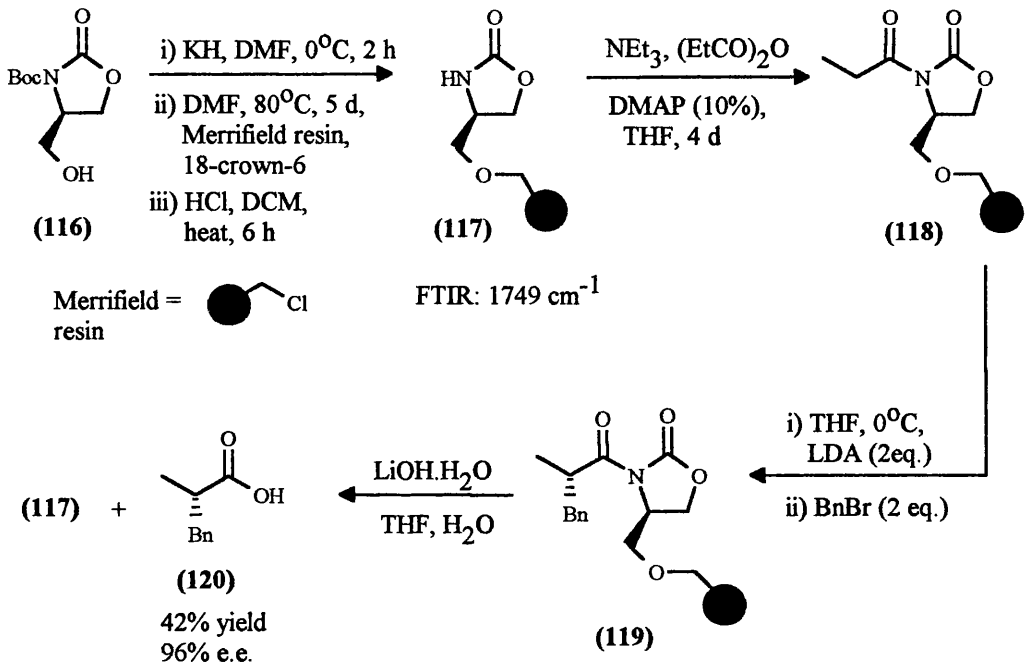
66% yield
Lit. 89% yield

This yield is significantly lower than the literature value**[149]** of 89% and our own crude yield of >90%. Furthermore, the Boc appendage does not offer any particular synthetic benefit and only serves to decrease the efficiency of the whole synthesis. Interestingly, these authors chose the Merrifield resin as the solid support as they reasoned the benzyl substituent would provide a high degree of steric bias in asymmetric synthesis. This view is opposite to our earlier conclusions where the steric bias is provided by an "internal" benzyl group, which is closer to the site of attack and is thus more effective as a chiral inducer.

The auxiliary was ether-linked onto the Merrifield resin via nucleophilic displacement of the benzylic chloride. Subsequent acidic deprotection unmasked the urethane nitrogen used for attachment to a potential substrate. No coupling yield or loading levels were given. Instead, FTIR spectroscopy was used to follow and confirm the attachment of the substrate as evidenced by the presence of extra carbonyl absorptions. In addition, the method of mixing was not disclosed. This is unfortunate as a literature**[281]** precedent indicates that good mixing is required for high conversion. Allin and Shuttleworth then used the triethylamine/DMAP(10%)/propionic anhydride system recommended by

Kunieda[282] and by Ager[174] for *N*-acylation. The *N*-acylated derivative **(118)** was deprotonated with LDA and the anion quenched with benzyl bromide before cleaving from the resin with lithium hydroxide. When used to prepare α-benzylpropionic acid **(120)**, the e.e. of the product was determined to be 96% using NMR techniques, but no optical rotation was given. The acid **(119)** was isolated in a questionable 42% yield (Scheme 54).

Scheme 54: Solid phase synthesis of α-benzylpropionic acid **(120)**



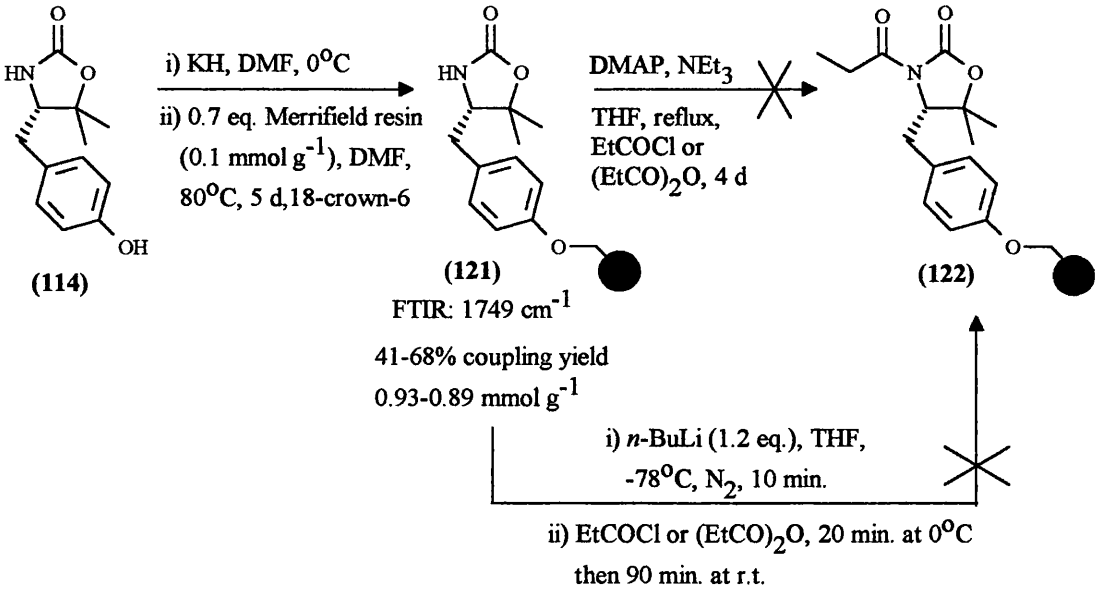
This yield is based on the undisclosed loading of the original Merrifield resin and seems to assume a 100% coupling yield with a 1:1 ratio of oxazolidin-2-one to Merrifield resin. However, the yield would be more creditable if it was based on a loading of the resin bound auxiliary instead. In this case, the value should be higher, given the loss of resin accompanying each transfer. This lack of information serves as a pertinent example where a communication, without a follow-up full paper, fails to meet the needs of experimentalists: many questions were left unanswered such as, was the auxiliary recycled, what were the effects of excess base and variation in

temperature? Nevertheless, this publication did show that solid phase asymmetric alkylation of Evans-type auxiliaries is possible. As a result, we determined to proceed as planned and expand our programme to cover Merrifield as well as Wang resins and investigate their suitability to solid phase alkylation reactions.

We began by following the conditions used by Allin and Shuttleworth to couple the trisubstituted oxazolidin-2-one **(114)** onto a Merrifield resin. This seemed to be successful as evidenced by FTIR spectroscopy and the weight gained was used as a means of estimating the reaction yield and the loading level of the resin. A coupling yield of 41-68% and a loading of 0.93-0.89 mmol g^{-1} were thus calculated.

Test acylation reactions with DMAP/NEt_3/propionic choride or anhydride (method A) and *n*-BuLi/propionic chloride or anhydride (method B) systems were carried out. Unfortunately the reactions failed as FTIR spectra of the product resin beads when crushed did not show the presence of a second carbonyl peak, which would characterize the resin-bound *N*-acylated oxazolidin-2-ones **(122)** (Scheme 55).

Scheme 55: Reactions involving resin-bound oxazolidin-2-one **(121)**



Further batches of the resin-bound auxiliaries **(121)** were synthesized and the yield improved by a second coupling reaction (up to 12% in some cases). These materials were combined and then capped**[38]** by converting the benzylic chloride to iodide, followed by radical reduction (Scheme 56).

Scheme 56

The capped resin-bound auxiliary was *N*-propionylated, but with limited success. As a check, the auxiliary was cleaved from resin using hydrogenation with palladium(II) acetate**[283]**. The ^{1}H NMR spectrum of the cleaved oxazolidinone showed the signals expected for the free NH component. The resonance of the NH group occurs at δ5.30. This result further supports the finding (from FTIR spectroscopy) that *N*-acylation did not occur. Lastly, only in one batch of capped resin-bound auxiliary did exhibit an IR spectrum with a weak band at 1672 cm^{-1}. However, after cleavage and on work up of this crude sample, no acylated product was obtained.

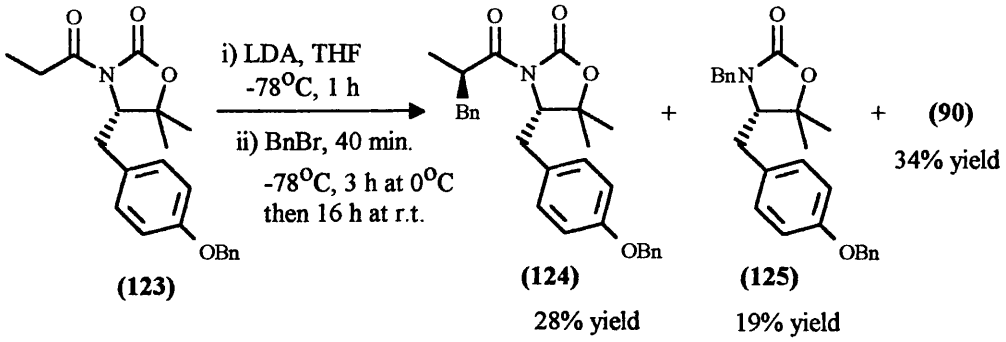
It is known that acylation is not a slow reaction, as a similar reaction in solution was completed within one hour without heating**[164]**. In our hands, however the attempted acylations on resins, repeatedly failed and these failures puzzled us. The logical approach would be the investigation of the behaviour of the oxazolidin-2-one off resin. This was next tried where the reaction is easily monitored.

3.6: Solution Phase α-Alkylation Reaction Study

The trisubstituted oxazolidin-2-one **(90)** was *N*-propionylated using *n*-butyl lithium and propionyl chloride to afford the appropriate product **(123)** in 93% yield. The IR

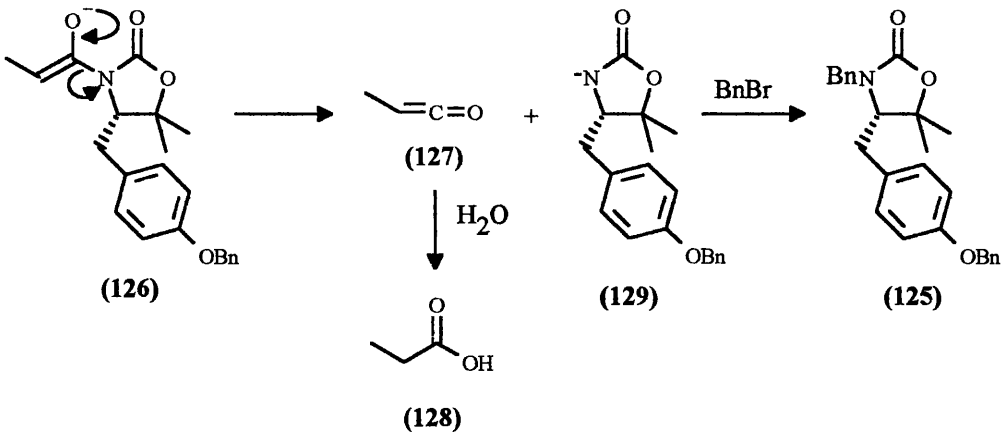
carbonyl absorption band associated with the propionyl group is 1770 cm^{-1} while that of urethane group is 1700 cm^{-1} . These bands are easily discernible and this confirms our earlier conclusions about the lack of reaction 'on resin'. Acylated oxazolidin-2-one **(123)** was enolised using LDA at -78°C and treated with benzyl bromide. Over several experiments, we obtained at best a 28% yield of the benzylated product **(124)**. Other side products were shown to be the *N*-depropionylated auxiliary **(90)** (34%) and the *N*-benzylated derivative **(125)** (19%) (Scheme 57).

Scheme 57: Benzylation of *N*-propionyloxazolidinone **(123)** at low temperature



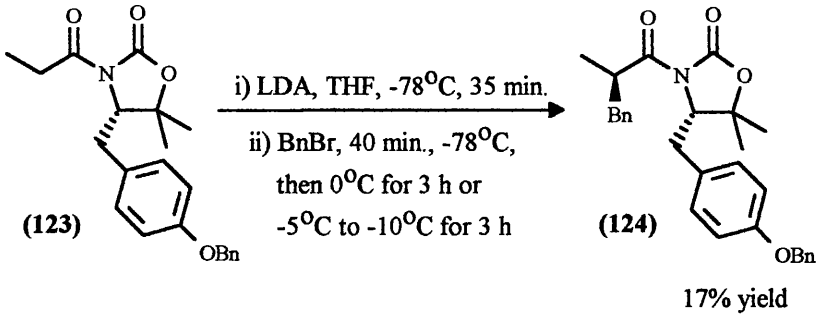
A change of base to LiHMDS did not make any difference to this result. No improvement in yield was observed if the time of reaction at lower temperature was increased. However, an increase in the yield of the *N*-depropionylated auxiliary **(90)** was observed if the reaction temperature was allowed to rise above 0°C for a prolonged period. Clearly, this is due to the instability of the enolate **(126)** at this temperature; this probably breaks down via a ketene**[182]**. The origin of the *N*-benzyl derivative **(125)** also seems obvious: the resulting oxazolidinone anion **(129)**, left after the loss of ketene **(127)**, is quenched by excess benzyl bromide (Scheme 58).

Scheme 58: Formation of *N*-benzylated oxazolidinone **(125)**



A fine balance has to be struck and a compromise in the reaction temperature is needed to obtain an optimum yield. The same problem was recognised by Kòll and coworkers**[164]** when they tried to alkylate an oxazolidinone derived from *D*-xylose. Kòll reported that a temperature between -25 °C and -15 °C maintained for 4 h was required for optimum alkylation. Even so, the yield these chemists claimed was a moderate 48%. We chose to work at higher temperatures, but for shorter periods in an attempt to increase the yield of our product. Despite our best laid plans, using the conditions summarised in the following equations, we obtained at best only a 17% yield of the benzylated compound **(124)** (Scheme 59).

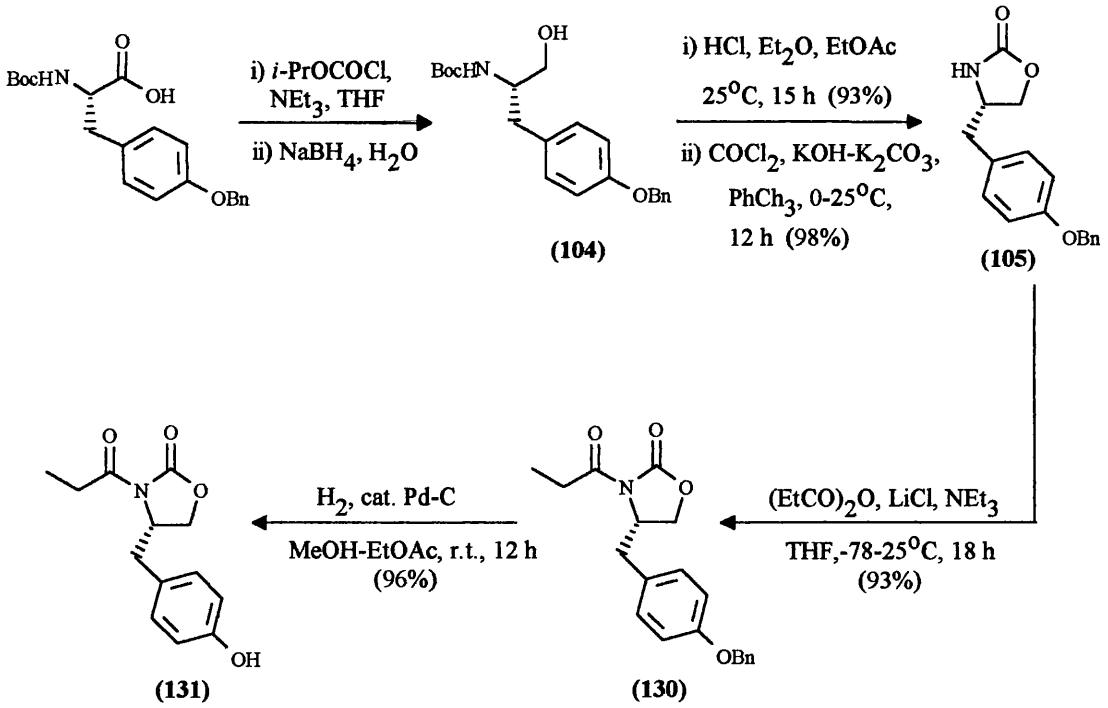
Scheme 59



During this time, a report by Burgess**[284]** on solid phase asymmetric alkylation was published, which had a profound impact on the direction of this project.

This work involved the preparation of the *N*-propionylated oxazolidin-2-one **(131)** and examined the yield and enantioselectivity of asymmetric alkylations of this auxiliary when supported on Merrifield, Wang and TentaGel R resins. The synthesis of oxazolidin-2-one **(105)** was similar to the our own route and started with (*S*)-*N*-Boc-*O*-benzyltyrosine. The carboxyl functional group was activated as a mixed anhydride, before reduction with sodium borohydride to give the *N*-Boc aminoalcohol **(104)**. The Boc group was removed and cyclized with phosgene to afford the heterocycle **(105)**. *N*-Propionylation was achieved using a triethylamine/lithium chloride/propionic anhydride system**[178]**. Finally the substrate was *O*-debenzylated, before being coupled to the resin (Scheme 60).

Scheme 60: Burgess' synthesis of 4-substituted oxazolidin-2-one **(105)**



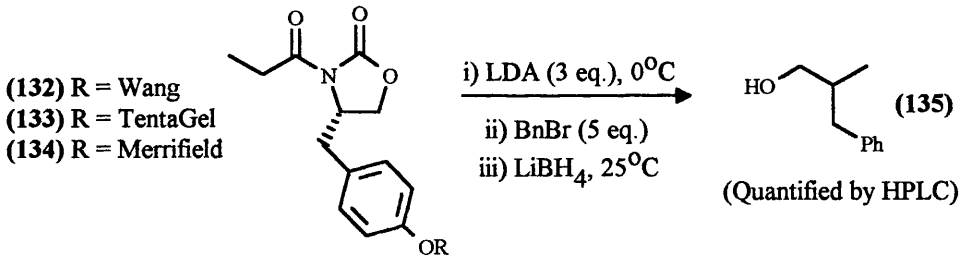
Next a Mitsunobu reaction (3 eq. of oxazolidinone **(131)**, DEAD, PPh_3, 20 h) was used to couple the auxiliary to a hydroxyl functionalized resin, either Wang or TentaGel R, whereas nucleophilic displacement was used to couple the auxiliary to a

Merrifield support[121] (3 eq. of **(131)**, Bu^tOK, cat. 18-crown-6, Bu_4NI, DMF, 75°C, 3.5 d).

The functionalized resins were cleaved with lithium benzyloxide to produce the propionate. The product was quantified using HPLC and NMR spectroscopy. From these results, a resin loading of 30% for the Merrifield resin was deduced against values of 56% and 60% for Wang and TentaGel systems respectively. The 56% loading compared favourably with our value of 51%.

In Burgess' group, the solid supported substrate was enolised with 3 equivalent of LDA at 0°C before the enolate was quenched with benzyl bromide (5 eq.). Different times were optimised for each resin and the coupling yields were quantified by HPLC analysis (Scheme 61).

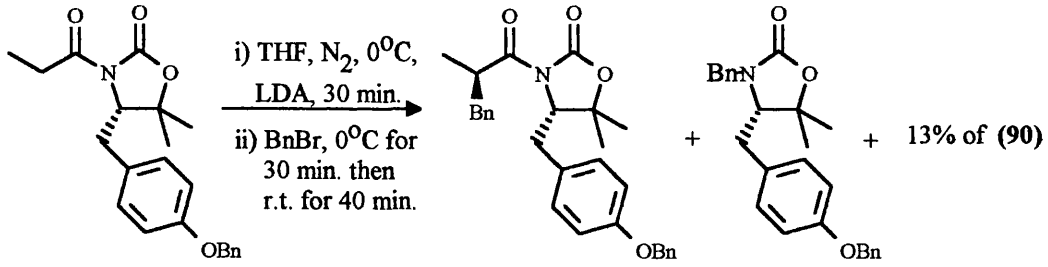
Scheme 61: General conditions for solid phase alkylation



The results obtained showed that the yield for the alcohol **(135)** was maximised in the initial stages of the reaction for all three resins. After this, the yield decreases in almost linear fashion as the reaction time is extended, this is entirely in keeping with our experience. For Burgess, the functionalized Wang resin **(132)** gave the alcohol **(135)** in a yield of 66% with an e.e. of 90% compared to ~50-60% e.e. from the Merrifield resin **(134)**. This stands in sharp contrast to the 96% e.e. obtained by Shuttleworth with their serine-derived oxazolidinone **(117)**. Burgess was surprised by this result since he believed the more substituted auxiliary should favour greater stereoselectivity.

Burgess's comprehensive study covers most of the initial objectives our project set out to achieve. Nevertheless, the alkylation reaction still needs optimization and this gave us encouragement to continue in our attempt to improve the overall process. For example, an important issue concerns the presence of *N*-alkyloxazolidin-2-one as a by-product. This will greatly hinder the recycling of the supported auxiliary should the process be used as originally intended. We took the solution of the decomposition problem of the enolate to be our major priority and *N*-propionyloxazolidin-2-one **(123)** was alkylated with benzyl bromide using Burgess's conditions to demonstrate its ability to function as a chiral auxiliary. The product **(124)** was obtained in 47% while deacylated **(90)** and *N*-benzylated **(125)** by-products were collected in 19% and 13% yields respectively (Scheme 62).

Scheme 62: Alkylation of *N*-propionyloxazolidinone **(123)** at 0°C



(123)
$[\alpha]_D^{20}$ -28
c = 1 in DCM

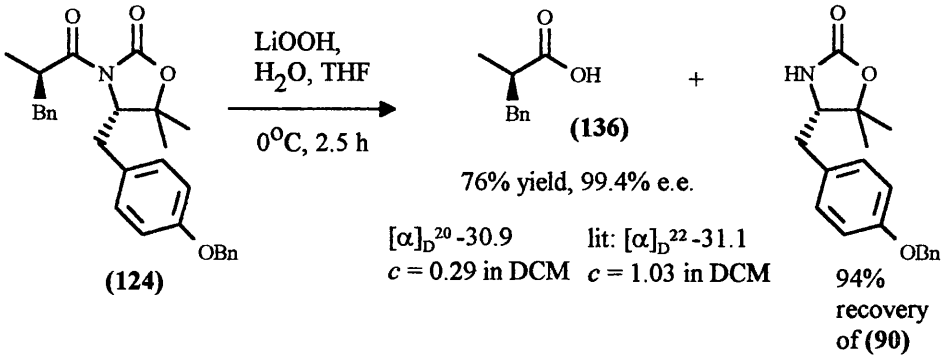
47% yield

(124)
$[\alpha]_D^{20}$ -58
c = 1.7 in DCM

(125)
19% yield

This result is comparable to the 51% yield obtained for the benzylation of propionic acid using 4-benzyl substituted SuperQuat**[150]** as the auxiliary. The resulting α-benzylpropionic acid **(136)** was recovered in 76% yield and exhibited $[\alpha]_D^{20} = -30.9$ (*c* = 0.29 in DCM) [(lit**[268]**: $[\alpha]_D^{22}$ -31.1 (*c* = 1.03 in DCM)] (Scheme 63).

Scheme 63

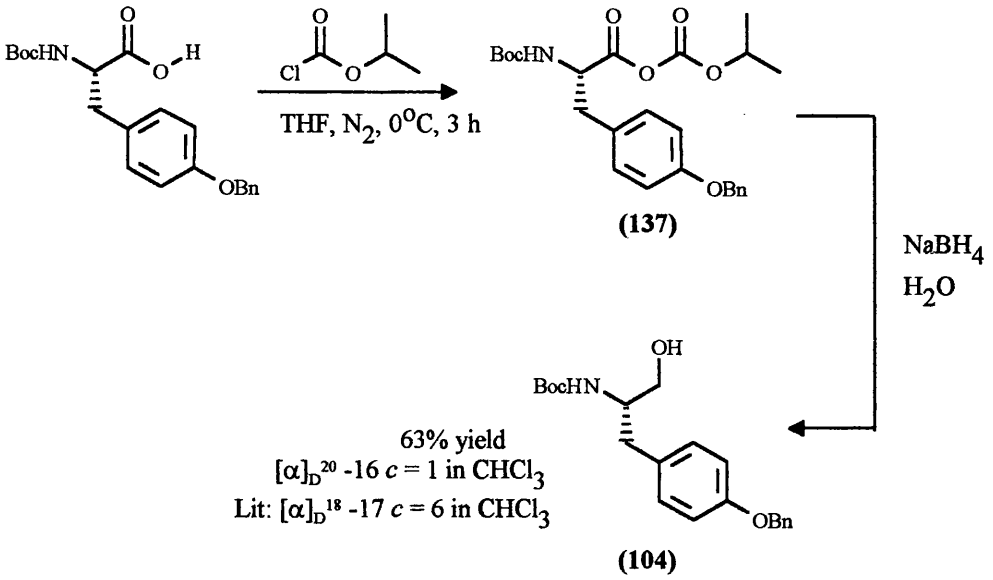


The optical purity of **(136)** is thus >99% if the literature value taken refers to the pure compound. The sense of stereochemical induction is readily interpreted by assuming a lithium chelated (*Z*)-enolate is generated, where diastereofacial attack occurred at the less hindered *si*-face. This result provided strong proof that the sterechemical integrity of the auxiliary is not compromised during its synthesis.

3.7: Optimization Study for Solution Phase α-Alkylation Reactions

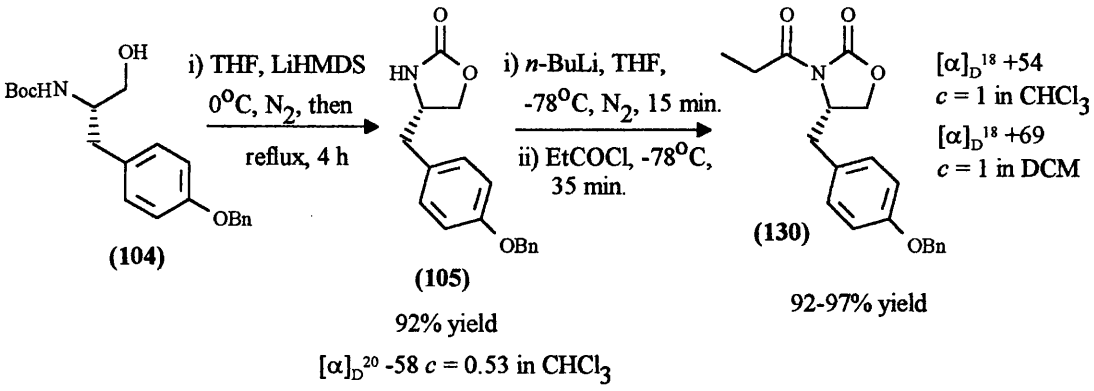
The unmethylated oxazolidin-2-one **(105)** was used for this study for ease of comparison with Burgess' results. Our initial route into this type of auxiliary is shorter than Burgess', but the yield in the reduction step of (*S*)-*N*-Boc-*O*-Bn tyrosine to the amino alcohol **(104)** is only a moderate 66%. We were interested to see if the American group's mixed anhydride technique offers a better method for activating and eventual reduction of the amino acid to the alcohol **(104)**. To establish this, the amino acid was treated with isopropyl chloroformate to form the mixed anhydride **(137)**. This product was reacted with sodium borohydride to give the amino alcohol **(104)** in 63% yield (Scheme 64).

Scheme 64: Reduction of amino acid using mixed anhydride/$NaBH_4$ method



Cyclisation to the heterocycle was then effected using our earlier conditions to give **(105)** in 92% yield (Scheme 65). The e.e. of product from both the American and our route was almost identical, but lower than that of a sample recently synthesised by Sudharshan**[278]**. Once prepared, the auxiliary **(105)** was tested in alkylation reactions to compare with the results obtained in solid phase. Propionylation with *n*-butyl lithium and propionyl chloride afforded acylated **(130)** in 92% yield after crystallization, or 97% after column chromatography (Scheme 65).

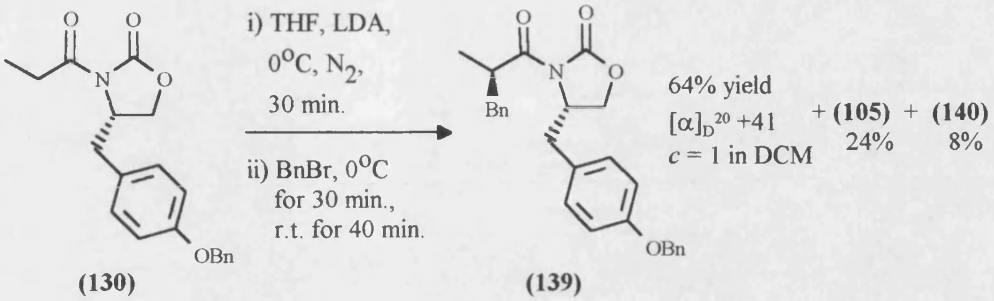
Scheme 65



This product was enolised with LDA at 0°C and the enolate was quenched with two different alkyl halides. The methylated product **(138)** was collected in an

unoptimised 16% yield. The α-benzylated product **(139)** was obtained in 64% yield when benzyl bromide was used (Scheme 66).

Scheme 66: Benzylation of *N*-propionylated oxazolidin-2-one **(130)**



The deacylated auxiliary **(105)** was recovered in 24% yield while the *N*-benzylated material **(140)** (~ 8%) collected as a mixture together with trace of **(130)**.

Once again we were confronted by the inherent instability of the enolate (a well documented problem), and in order to find a solution to it we attempted an inverse addition**[286]** of benzyl bromide to the enolate (Scheme 67) and Table 9.

Scheme 67: Inverse alkylation of the 4-substituted oxazolidinone **(130)**

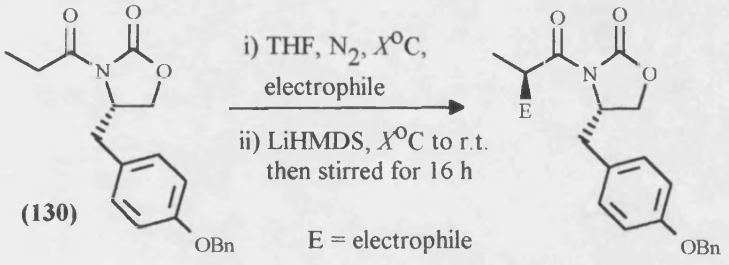


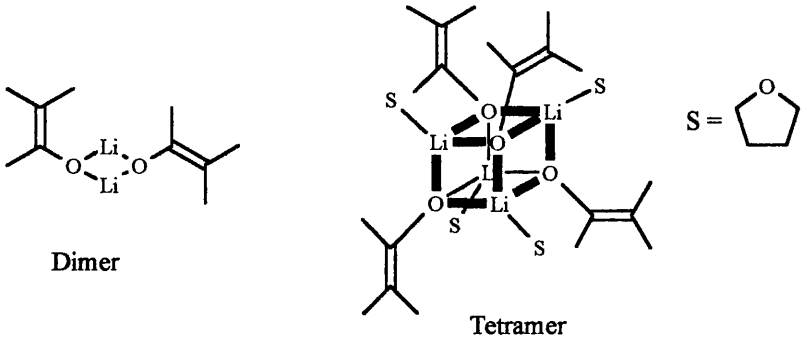
Table 9: Yield of alkylation at difference reaction temperatures

	Benzyl bromide
0°C to r.t.	Product (62%), *N*-Bn product (18%) & deacylated auxiliary (7%)
-78°C to r.t.	Product (72%), *N*-Bn product (9%) and deacylated auxiliary (3%)

A higher yield of 72% versus 62% and fewer side products were obtained at lower temperature for benzyl bromide.

It is well documented that polar metal enolates, particularly lithium enolate, exit as aggregates**[287-290]** in solution. The degree of aggregation is solvent dependent and could be oligomeric (dimer or tetramer) or polymeric in nature (Figure 11).

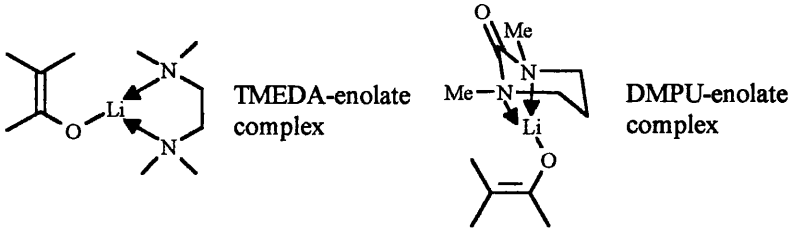
Figure 11



These intermediates impart significant steric hindrance as the electrophiles attack the enolate through the Bùrgi-Dunitz trajectory angle of 110°. However, the lithium enolates can be deaggregated by adding lithium chloride**[287]**, or cation solvators/Lewis bases like tetramethylethylenediamine**[291-2]** (TMEDA) and dimethylpropyleneurea (DMPU)**[293-4]**.

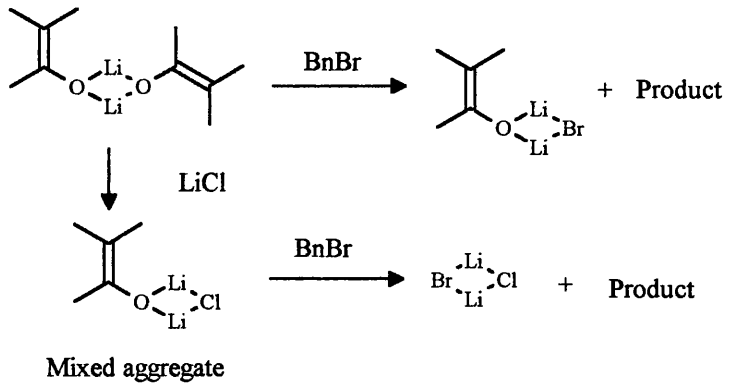
The Lewis base acts by breaking up the pure aggregates, but also prevents reaggregation due to the steric bulk it imparts onto the lithium cations (Figure 12).

Figure 12: Complexation of Lewis bases to lithium enolate



Lithium chloride also breaks down the bulky aggregates, but forms a more reactive mixed aggregates. In this way, the reaction is more efficient as no enolate is left unconsumed (Figure 13).

Figure 13: Effect of LiCl on reaction pathway and product distribution



Apart from these effects, the additives also increase the polarity of the solvent and the electron density around the π bond, thus increasing the rate of reaction.

We tested DMPU and lithium chloride in an attempted to accelerate our benzylation reaction, but disappointingly no improvement was observed. It should be noted that Meyer**[295]** has reported that lithium chloride fails to accelerate reactions where primary alkyl halides are involved. These results are in accord with earlier studies dealing with the use of lithium imide enolate, where its limited reactivity restricts the choice of electrophile to S_N2 active species like methyl, allyl and benzyl bromide **[296]**. This prompted us to investigate other enolate systems, where the alkylation reaction might proceed at a convenient rate and high chiral transfer.

3.8: Enolates studies

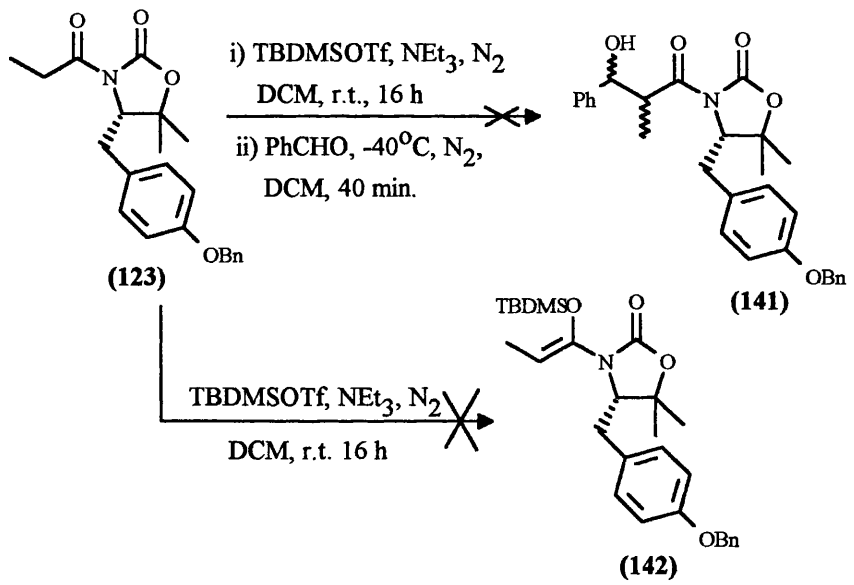
3.8.1: Silyl enol ethers

Silyl enol ethers are nucleophilic **[297-9]** and they have been used previously in S_N1 alkylations of carbonyl compounds **[296]**. Furthermore, certain silyl enol ethers are

stable enough to be isolated at room temperature **[300-1]**. This feature provides an attractive option. Preliminary silylation reactions had been carried out earlier using the 5,5-dimethyloxazolidin-2-one **(123)**.

Tert-butyldimethylsilyl triflate (TBDMSOTf) has been utilised by Oppolzer**[300]** as the silylating and internal Lewis acid catalyst for the aldol reaction. We considered this reagent might also activate the silyl enol ether formed in our reaction towards alkylation. A test enolisation and aldol reaction was carried out to assess the viability of this method (Scheme 68).

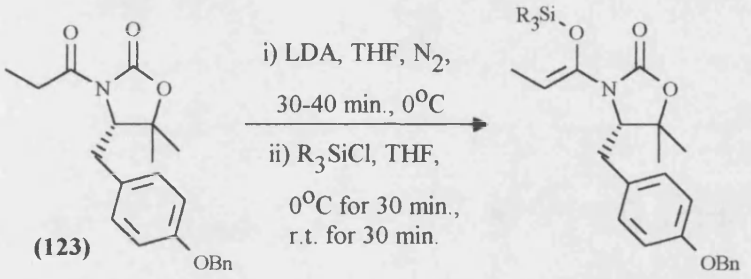
Scheme 68



Oxazolidin-2-one **(123)** was treated with *tert*-butyldimethylsilyl triflate (TBDMSOTf) and triethylamine in deuterated dichloromethane for 16 h under an inert atmosphere. The crude mixture was analysed directly by 400 MHz ^{1}H NMR spectroscopy. Sadly, the enol ether was not detected as evidenced by the absent of signals belonging to the vinylic methine (quartet~δ4-δ6) and methyl (doublet ~δ1.5-δ2) protons. Even so, the reaction mixture was treated with benzaldehyde at -78°C under an inert atmosphere, as expected a large amount of starting material **(123)** and

Lewis acid assisted *O*-debenzylated product **(143)** were recovered after workup. The enol ether forming reaction was repeated with LDA and with sodium bis(trimethylsilyl)amide as bases and, again an attempt was made to trap with different silylating reagents (Scheme 69). The results of these reactions are summarized in Table 10. A non-aqueous work up of the reaction mixture involving *in vacuo* removal of solvent was adopted before NMR analysis.

Scheme 69: Silylation of the imide enolate with TMSCl, TBDMSCl and TBDPSCl



Base = LDA or NaHMDS
R_3SiCl = TMSCl, TBDMSCl and TBDPSCl

R = TMS **(144)**
R = TBDMS **(142)**
R = TBDPS **(145)**

Table 10: Results of silylation reactions

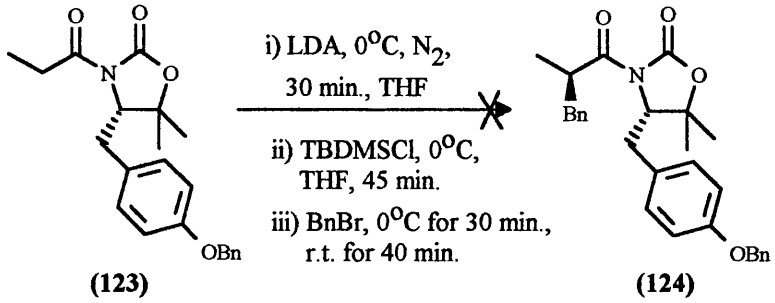
Silylating reagent	LDA	NaHMDS
TMSCl	No product detected	N/A
TBDMSCl	No product detected	N/A
TBDPSCl	Product detected (4% yield).	Product detected by NMR only.

No silyl enol ether was formed for the less bulky silylating reagents. However, a change in NMR spectra was detected when *tert*-butyldiphenylsilyl chloride (TBDPSCl) was used with either of the bases. A large chemical shift (~ δ0.5-δ0.7) was observed for the aromatic methine protons of tyrosine. The reaction was repeated on a larger scale and, after chromatography, the product **(145)** was collected as a mixture with the *N*-acylated auxiliary **(123)**. The total yield was 4% based on integration of the ^1H NMR spectrum. In this, the vinylic methyl resonances could be

seen in the highfield region (δ1.41) of the spectrum and moreover, a proton-proton decoupling experiment revealed that the α-CH and β-CH_2 protons were intact. This result discounted the possibility of the silyl group being attached elsewhere in the molecule. The ^{13}C NMR spectrum was equally informative. The signal of the vinylic methyl group was visible at δ19.8 (δ17.5 for *tert*-butyldimethylsilyl enol ether derived from 4-isopropyloxazolidin-2-one)**[302]** while the absence of methylene carbon signals from the propionyl group further supported the enol ether's presence. Furthermore, the resonance of the carbon nuclei from the silyl group were clearly visible.

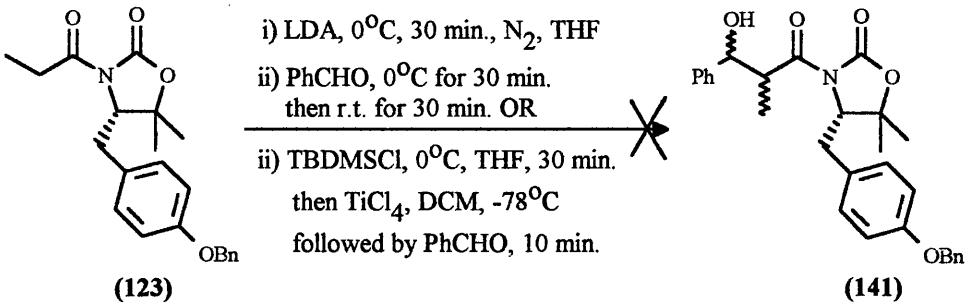
The low yield in the reaction, however, renders this particular silyl enol ether an unsuitable intermediate. Before moving to another metal counter ion, we decided to re-examine the *tert*-butyldimethylsilyl enol ether. Although not isolated, the silyl enol ether might exit as a transient species in the solution, where it could still participate in the reaction. Three experiments were performed to test this theory. In the first experiment, benzylation was attempted in the presence of TBDMSCl (Scheme 70), while in the second and third experiments, both catalysed and non-catalysed aldol reactions were attempted (Scheme 71).

Scheme 70



(123) **(124)**

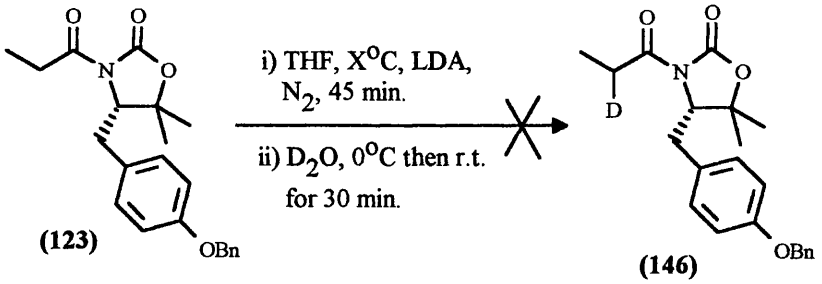
Scheme 71



(123) **(141)**

In all cases, the desired products were not detected. Unreacted material **(123)**, deacylated auxiliary **(90)** and unidentified impurities were all that was found in the reaction mixtures. D_2O exchange experiments were then carried out to test the degree of deprotonation. This was necessary in order to explain the high level of unreacted material after various attempts. Surprisingly, no deuterium incorporation was observed as evidenced from the NMR spectra of the starting material (Scheme 72).

Scheme 72: Attempted α-deuteration of *N*-propionyloxazolidin-2-one **(123)**

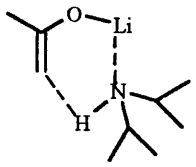


(123) **(146)**

X = 0°C or -10°C

This type of result has been reported**[287]** previously by other workers and is explained in terms of a secondary amine effect. A qualitative explanation involved proton abstraction by LDA to generate diisopropylamine. This amine then complexes and hydrogen bonds with the lithium enolate as shown in Figure 14.

Figure 14: Possible lithium enolate-diisopropylamine complex



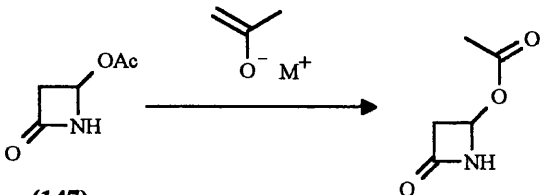
When quenched with D_2O, intramolecular proton transfer from the diisopropylamine competes successfully with the intermolecular attack of the deuterium**[303]**. This then regenerates the starting material without deuterium labelling.

These unsuccessful results combined with the shortage of time severely limited the options available to us, Within the remaining time, we therefore decided to widen our coverage of metal cations at the expense of a further in-depth *O*-silylation study.

3.8.2: Zinc, Boron and Tin enolates

The use of zinc, boron and tin enolates in S_N2 displacement reactions is well documented in the synthesis of β-lactam antibiotics**[304-6]**. Here the key step of the synthesis involves the reaction of a metal enolate with an acetoxyazetidinone **(147)** (Scheme 73).

Scheme 73: Use of metal enolates in the synthesis of β-lactam antibiotics

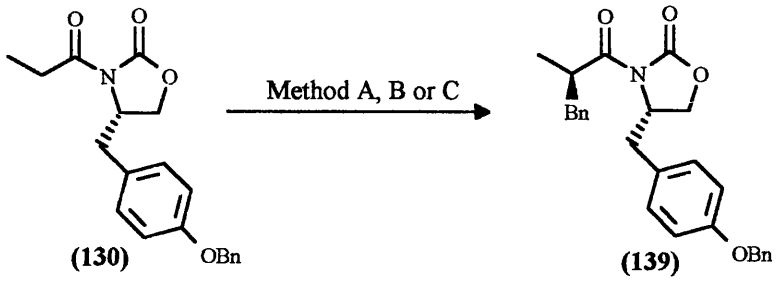


(147) **(148)**

The required enolates are generally prepared via transmetalation or directly at temperatures close to 0°C. The similarities between the conditions used for the generation of these enolates thus prompted us to investigate similar reactions with our substrate. A variety of conditions were employed for benzylation reaction using

boron, zinc(II), Sn(II) and Sn(IV) enolates of the *N*-acyloxazolidin-2-one **(130)** (Scheme 74) and (Scheme 75).

Scheme 74: Conditions for benzylation using zinc and enolates



Method A

i) LDA, THF, 0°C, N_2, 30 min.

ii) $ZnBr_2$, THF, 10 min.

iii) BnBr, 0°C for 30 min. or 6 h then r.t. for 30 min.

Method B

i) *n*-Bu_2BOTf, NEt_3, 0°C, N_2, 2 h

ii) $ZnBr_2$, THF, DCM

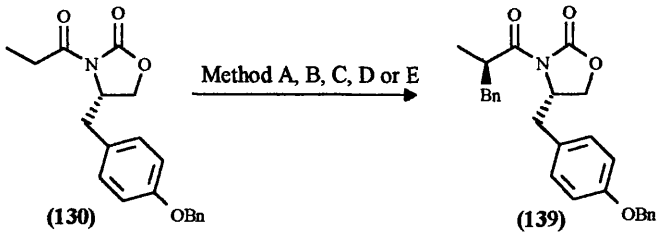
iii) BnBr, 0°C for 30 min. or 3 h then r.t. for 30 min.

Method C

i) *n*-Bu_2BOTf, *i*-Pr_2NEt, 0°C, N_2, 2 h ii) $ZnBr_2$, THF, DCM

iii) BnBr, 0°C for 30 min. then r.t. for 30 min.

Scheme 75: Conditions for benzylation using tin enolates



Method A

i) *N*-ethylpiperidine, THF, -5°C, N_2, 5 min.

ii) $Sn(OTf)_2$, THF, 4 h iii) BnBr, -5°C for 2 h

Method B

i) $Sn(OTf)_2$, *i*-Pr_2NEt, 0°C, N_2, 3 h

ii) $ZnBr_2$, THF iii) BnBr, 0°C for 30 min. then r.t. for 30 min.

Method C

i) LDA, THF, -5°C, N_2, 30 min.

ii) $Sn(OTf)_2$, THF, 10 min. iii) BnBr, -5°C for 30 min. then r.t. for 30 min.

Method D

i) LDA, THF, 0°C, N_2, 30 min.

ii) Ph_3SnCl (0.4 eq. or 1 eq.), THF, 10 min.

iii) BnBr, 0°C for 30 min. then r.t. for 30 min.

Method E

i) LDA, THF, 0°C, N_2, 30 min.

ii) Ph_3SnCl, THF, 10 min.

iii) Bu_4NBr, THF, 0°C, 10 min.

iv) BnBr, 0°C for 30 min. then r.t. for 30 min.

Disappointingly, the boron enolate failed to produce the desired benzylated product **(139)** and the *N*-propionylated auxiliary was recovered as the only reaction component. As for the zinc enolate, the deacylated material was collected in 45-48% yield together with the starting material **(130)**.

For the tin(II) enolate, no reaction occurred when *N*-ethylpiperidine or diisopropylethylamine and tin triflate were used as base and tin(II) cation sources. Whilst the other tin(II) enolate/alkylation reaction provided starting material **(130)** and deacylated by-product **(105)**.

Tin(IV) enolate alkylation reactions were more successful than the previous reactions as the benzylated product **(139)** was formed in 20-40% yields. In addition, the amount of unreacted starting auxiliary **(130)** recovered was reduced (Scheme 75). Even in this procedure however, the product collected was contaminated with a tin impurity. This proved impossible to remove. Attempts were made to convert this impurity into an insoluble fluoride salt**[307]** or water-soluble hydroxide**[308]**, but these attempts were to no avail. Thus, despite early promise, this problem renders the use of the tin(IV) enolates unattractive.

A promising approach was discovered at the end of the project and it involves the use of the Ti(IV) enolate as recommended by Evans**[186]**. The Ti(IV) enolate was generated from the *N*-propionyloxazolidinone by treating it at 0°C in DCM with $TiCl_4$ or isopropyl titanium trichloride and diisopropylethylamine or NEt_3. Thermal decomposition of the enolate at 0°C does not occur so this mode of enolate formation is very attractive.

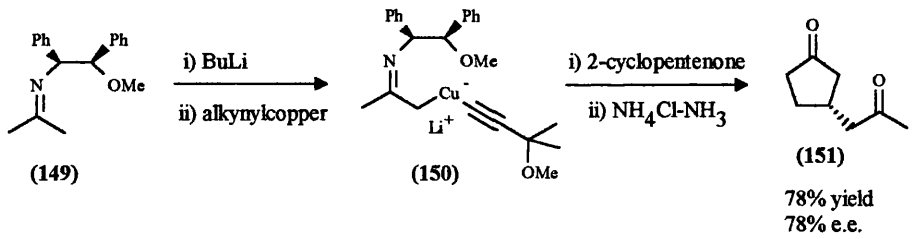
Interestingly, Evans noted that in the formation of the enolate, time must be allowed for the Lewis acid-substrate complex to form before the base is added. Otherwise $TiCl_4$ complexes irreversibly with the base and as a consequence, no enolisation

occurs. A similar interaction might also operate in the boron, zinc(II) and Sn(II) enolate alkylation reactions in which a tertiary amine base was used. This would then explain the almost quantitative recovery of the substrate in some cases. We cannot verify this conclusion, however, with the evidence in hand.

3.9: Conjugate Addition Reactions

Some work in conjugate addition was launched around the same time as the metal enolate studies. The objective was to investigate the use of a chiral enolate as a transferable ligand in organocuprate conjugate addition. This particular approach to asymmetric conjugate addition is not well explored. Nevertheless, Tsuji and workers[309] did achieve good yield and e.e. using a chiral azaenolate as the transferable ligand (Scheme 76).

Scheme 76



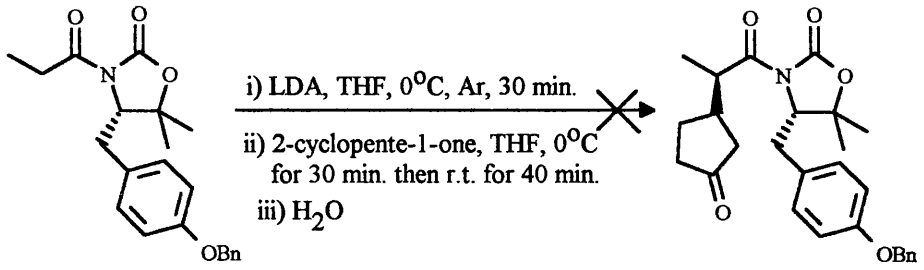
(149) (150) (151)

78% yield
78% e.e.

More specifically, it was hoped that the chirality at the α-position could be controlled by the presence of a chiral unit appended at the β-position. If successful, three contiguous stereogenic centres can be created in one step. Such three component reactions, or so called conjugate addition-enolate trapping reactions[310], have many synthetic applications. Most noticeably in the synthesis of biologically active natural products such as prostaglandins[311-2] and terpenoids[313-4].

A model reaction was set up to examine if the enolate from *N*-acylated oxazolidinone **(123)** could be reacted with 2-cyclopenten-1-one (Scheme 77).

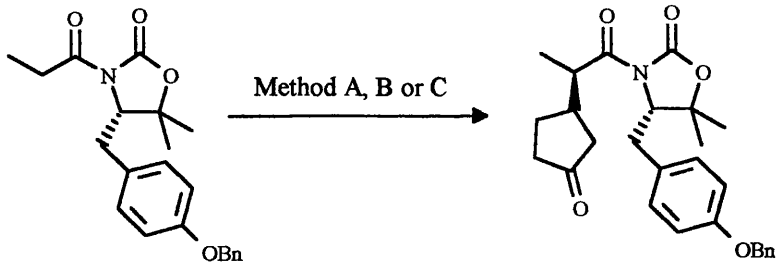
Scheme 77



(123) **(152)**

Unfortunately this failed and the *N*-deacylated oxazolidinone **(90)** was the main product recovered. Several other test reactions were carried out in which the lithium enolate was treated with lithium 2-thienylcyanocuprate or copper(I) cyanide before reacting it with 2-cyclopenten-1-one (Scheme 78).

Scheme 78: Attempted conjugate addition with organocuprate reagents



(123) **(152)**

Method A: i) LDA, THF, 0°C, Ar, 35 min. ii) LiCuCN(2-Th), THF, 0°C, 35 min. then r.t. for 10 min. iii) 2-cyclopenten-1-one, -40°C for 2 h then 0°C for 160 min.

Method B: i) LDA, THF, 0°C, N_2, 30 min. ii) LiCuCN(2-Th), THF, 0°C for 2 or 4 h iii) 2-cyclopenten-1-one, -40°C for 2 h then 0°C for 4 or 2 h

Method C: i) LDA, THF, 0°C, N_2, 65 or 45 min. ii) CuCN, THF, 0°C for 75 or 90 min. iii) 2-cyclopenten-1-one, 0°C for 6 h or 1 h

Cuprate additions to enones are, of course extremely well known and such reagents and conditions are well advertised**[310]** to ensure that the cuprate equivalent forms from the lithium enolate.

Analysis of mixtures formed after the above reactions were carried out, proved that starting material and deacylated auxiliary were the major recoveries. The failure of these reactions could be due to either no organocuprate formation or low transfer rate of the enolate ligands to the enone system. The recovery of the *N*-propionyloxazolidin-2-one **(123)** suggests the former. Further investigation into this matter was curtailed by lack of time, however, a simpler approach involving the addition of Ti(IV) enolate might be feasible. As mentioned in the previous section, Evans had successfully employed the Ti(IV) enolate generated from *i*-$PrOTiCl_3$ or $TiCl_4$/DIPEA system in Michael additions. Ultimately, the viability of this approach can only be determined experimentally.

Summary II

Derivatives of 'second generation' or 5,5-disubstituted oxazolidinones are highly crystalline and suited to both solid, but especially to solution phase synthesis. However, 'first generation' or Evans's original oxazolidinones perform equally well. In addition, they can be prepared in fewer synthetic steps. Therefore the type of resin-bound oxazolidinone used here depended upon the nature of the substrate.

Merrifield resin-bound oxazolidin-2-one was synthesized with a coupling yield of 41-68% using nucleophilic displacement. *N*-Acylation of this polymeric reagent was attempted but without any success. A model study using Fmoc-Tyr-OMe suggested the Mitsunobu reaction is a superior method for the attachment of oxazolidin-2-ones. Although an average coupling yield of 47% was obtained for the Wang resin-bound Fmoc-Tyr-OMe, the reaction time is much shorter, and the condition is milder. The same conclusions can be applied to the capping procedure for the two different resins. Finally, the loading levels of the functionalised polymers are increased if subjected to a second coupling reaction.

During the course of the project, the use of resin-bound oxazolidin-2-ones in alkylation reactions was studied. Model alkylation of propionic acid with benzyl bromide was achieved with a moderate yield (42%-72%) and good to excellent e.e. (97-99%). However, low yields and unsatisfactory enantiomeric excesses were obtained for other electrophiles. More importantly, thermal decomposition of lithium imide-enolates under the reaction conditions was a constant problem. As a result, the recycling potential of this procedure is compromised. The replacement of the lithium cation with titanium or other metal ions is a possible way forward. Despite recent advances, the concept of a reusable solid-supported auxiliary is still unfulfilled and further optimisation of this approach is required to realise this goal.

Lithium enolates, derived from *N*-acyloxazolidinones, were investigated as transferable ligands of organocuprate reagents in conjugate addition reactions but such addition reactions using two organocuprate forming systems failed. Thermal instability and bulkiness of the lithium enolates may disfavour the organocuprate formation and hence explain the results. Nonetheless, an extension of its chemistry into conjugate addition reactions looks promising and warrants further study.

Experimental

General

Anhydrous diethyl ether and THF were obtained by distillation under nitrogen from sodium-benzophenone ketyl, toluene from sodium and dichloromethane from calcium hydride. Petroleum ether, b.p. 60-80°C and ethyl acetate were distilled prior to use in chromatography. All commercial reagents were used without further purification unless stated otherwise. Reagents were purified according to procedures described in Vogel **[315]** or Perrin and Perrin**[316]**. The concentation of *n*-butyl lithium was titrated with 4-biphenylacetic acid**[317]** before use. Flash chromatography was performed under medium pressure using matrex 60Å Silica or Merck Kieselgel 60. Reactions were monitored by TLC on Whatman aluminium backed UV_{254} silica gel plates or Merck glass backed Kieselgel 60 F254 fluorescent plates. Melting points (m.p.) were recorded on an Electrothermal apparatus or Bucchi 535 melting point apparatus and are uncorrected. Optical rotations were measured with an AA-10 automatic polarimeter from Optical Activity Ltd. or a Pekin-Elmer 141 polarimeter calibrated with sucrose (10 mg/ ml, $[\alpha]_D$ = 66.7). Concentrations (*c*) are given in g 100 ml^{-1}. Proton magnetic resonance spectra (^1H NMR) spectra were recorded at 270MHz on a JOEL GX 270 spectrometer, at 400 MHz on a JOEL GX 400 or a Bruker ARX 400 spectrometer with QNP probe and 32 scans. Carbon magnetic resonance spectra (^{13}C NMR) spectra were recorded at 100 MHz on a JOEL JNM instrument or at 400 MHz on a Bruker ARX 400 spectrometer with 1032 scans. The assignment of ^{13}C spectra was assisted by DEPT experiments. All *J* values are recorded in hertz. Low resolution mass spectra (FAB) were recorded on a VG 7070E instrument with NBA used as the matrix. Electrospray

mass spectra were recorded on a VG Trio-2000 spectrometer in positive mode. Microanalysis was performed by A. K. Carver, School of Chemistry, University of Bath.

IR spectra were recorded on a Perkin-Elmer 1605 or a Nicolet Avatar 360 FTIR spectrometer using NaCl plates or as KBr discs. UV readings were recorded on a Pye Unicam PU8800 UV/ VIS spectrophotometer. HPLC analysis was performed on HP series 1100 machine.

The attempted synthesis[149] *of (S)-4-methoxycarbonyl-2-oxazolidinone* **(39)** *using phosgene*

Part a: *With water as solvent*

(*S*)-serine methyl ester hydrochloride (3.48 g, 21.9 mmol) and potassium hydrogen carbonate (2.70 g, 27 mmol) were dissolved in water (30 ml). The solution was stirred for 10 min. at r.t. before potassium carbonate (4.60 g, 33.6 mmol) was added. The temperature was cooled to 0°C and a solution of 20% phosgene in toluene (14 ml, 26 mmol) was added slowly dropwise. After five hours of stirring at 0°C, the aqueous layer was separated and the solvent removed to give a white solid which was extracted with dichloromethane (2 x 50 ml). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to the title compound **(39)** as a yellow oil (22 mg, 0.7%). δ_H (270 MHz, $CDCl_3$) 6.28 (1H, s, N*H*), 4.62 (1H, t, *J* 9, C*H*), 4.54 (1H, dd, *J* 9, 5, CH*H*), 4.4 (1H, dd, *J* 9, 5, C*H*H), 3.83 (3H, s, OCH_3).

Part b: *With increase equivalence of phosgene*

Same procedure as above. The quantities of reagents used were as followed: (*S*)-serine methyl ester hydrochloride (590 mg, 3.78 mmol), potassium carbonate (580 mg, 4.22 mmol), potassium bicarbonate (416 mg, 4.16 mmol) and 20% phosgene in

toluene (2.7 ml, 5.1 mmol). The oxazolidin-2-one **(39)** was obtained as an oil (191 mg, 28%). δ_C (100 MHz, $CDCl_3$) 170 ($CO_2\underline{C}H_3$), 159 (O-$\underline{C}$O-N), 66.6 (O$\underline{C}H_2$), 53.6 ($\underline{C}$H), 52.8 (O$\underline{C}H_3$); δ_H (270 MHz, $CDCl_3$) 6.87 (1H, s, N$\underline{H}$), 4.56 (1H, t, *J* 10, C$\underline{H}$), 4.46 (1H, d, *J* 4, C$\underline{H_2}$), 4.43 (1H, d, *J* 5, C$\underline{H_2}$), 3.94 (3H, s, $CO_2C\underline{H_3}$); ν_{max} ($CHCl_3$)/cm^{-1} 3318 (CO_2CH_3), 1739 (O-CO-N).

Part c: *Attempted synthesis in dichloromethane at 0°C*

Distilled triethylamine (1.08 ml, 7.74 mmol) was added to a solution of methyl ester (400 mg, 2.58 mmol) in dichloromethane (10 ml) under N_2 atmosphere with stirring. After 15 min., the reaction was cooled to 0°C and a solution of 20% phosgene in toluene (1.60 ml, 3.1 mmol) was added dropwise. The reaction was stirred at 0°C for 18 hours. Water (15 ml) was added and the organic layers were combined, washed with 1M hydrochloric acid solution (25 ml), saturated $NaHCO_3$ solution (25 ml), brine (25 ml), dried ($MgSO_4$) and filtered. The solvent was removed to yield a yellow oil (138 mg). ^1H NMR analysis indicated a mixture which did not contain the desired product.

Part d: *Attempted synthesis in dichloromethane at -78°C*

Same procedure as Part c but the temperature was lowered to -78°C. Quantities of reagents used were as followed: (*S*)-serine methyl ester hydrochloride (1.00 g, 6.43 mmol), triethylamine (2.7 ml, 19.4 mmol), distilled dichloromethane (20 ml) and 20% phosgene in toluene solution (4.1 ml, 7.75 mmol). The reaction was stirred for 2 h before workup. A yellow oil was obtained and its TLC (50% EtOAc in light petroleum ether 60-80°C) showed a complicated mixture that included starting material after treatment with ninhydrin. The reaction was abandoned.

Part e: *Attempted synthesis in dichloromethane at reflux*

Triethylamine (2.7 ml, 19.4 ml) was added to a stirred suspension of (*S*)-serine methyl ester hydrochloride (1.00 g, 6.34 mmol), in dry dichloromethane (20 ml) under N_2 atmosphere. After 5 min., 20% phosgene in toluene solution (4.1 ml, 7.75 mmol) was added slowly to the mixture which was stirred at r.t. for 90 min. before refluxed for 2 h. The TLC of the mixture again showed a complicated mixture. The reaction was discontinued.

The synthesis of (S)-4-methoxycarbonyl-2-oxazolidinone **(39)** *with lyophilized workup*

Potassium hydrogen carbonate (7.96 g, 79.5 mmol) was added to a stirred suspension of (*S*)-serine methyl ester hydrochloride (11.8 g, 75.8 mmol). After 10 min., potassium carbonate (11 g, 79.6 mmol) was added and the temperature cooled to 0°C. Solution of 20% phosgene in toluene (53.5 ml, 101 mmol) was slowly added into the mixture and stirred at 0°C for 2 h. The aqueous layer was separated and lyophilized. The resultant solid was washed with dichloromethane (3 x 100 ml) and the organic layers were combined, dried ($MgSO_4$), filtered and solvent removed to give the crude **(39)** as a yellow oil (9.20 g, 63.4 mmol, 84%). Vacuum distillation (230°C, 0.7 mmHg) using a Kugelrohr apparatus afforded an oil which solidified on standing to give a white solid (7.61 g, 69%). ν_{max} ($CDCl_3$)/cm^{-1}: 3298 (CO_2CH_3), 1768 (O-CO-N, CO_2CH_3); δ_H (400 MHz, $CDCL_3$) 6.76 (1H, s, N*H*), 4.62 (1H, t, *J* 9, C*H*), 4.52 (1H, dd, *J* 9, 5, CH*H*), 4.46 (1H, dd, *J* 9, 5, C*H*H), 3.82 (3H, s, OC*H*$_3$); δ_C (400 MHz, $CDCL_3$) 170.7 (*C*O_2CH_3), 159.3 (O-*C*O-N), 67.2 (O*C*H_2), 54.2 (*C*H), 53.5

($\underline{C}H_3$); m/z (ES+): 146 (M+1, 100%); $[\alpha]_D^{20}$ -21 (*c* = 0.5 DCM) Lit**[149]**:$[\alpha]_D^{25}$-18.6 (*c* = 4.52, DCM).

The attempted formation of 4-methoxycarbonyl-2-oxazolidinone **(39)** *using diethyl carbonate* **[169]**

Part a: *With ethanol as solvent and potassium carbonate as base*

Dry ethanol (20 ml) was added to a mixture of (*S*)-serine methyl ester hydrochloride (4.00 g, 25.7 mmol) and anhydrous potassium carbonate (4.26 g, 30.8 mmol) under N_2 atmosphere with stirring at r.t.. The mixture was stirred for 10 min. before diethyl carbonate (9.3 ml, 76.8 mmol) was added. A Vigreux column equipped with distill head, thermometer, condenser, receiver head and receiver flasks with nitrogen gas inlet were quickly assembled. The reaction mixture was refluxed for 10 h at 130°C. Colour of the reaction mixture changed from colourless to brown as the distillation proceeded. The mixture was diluted with dichloromethane (120 ml) and washed with water (150 ml). The aqueous layer was separated and washed with dichloromethane (2 x 100 ml). The organic layers were combined, dried ($MgSO_4$), filtered and solvent removed to yield a brown oil (138 mg). The ^1H NMR spectrum the oil indicated the presence of starting material, diethyl carbonate and possibly product (~50% yield based on a splitted singlet around the methyl ester region of δ 3.73).

Part b: *With dichloromethane as solvent and triethylamine as base*

Triethylamine (1.1 ml, 7.89 mmol) was added to a suspension of (*S*)-serine methyl ester hydrochloride (1.00 g, 6.43 mmol) in dry dichloromethane (20 ml) under N_2 atmosphere with stirring at r.t.. After 10 min., diethyl carbonate (1.60 ml, 13 mmol)

was added and the mixture was stirred for 16 hours. More diethyl carbonate (1.6 ml, 13 mmol) was added and stirred for 4 h before being heated at 40°C for 1 h. The reaction mixture was washed with water, 1 M hydrochloric acid solution, saturated sodium bicarbonate solution and saturated brine solution. The organic layer was dried ($MgSO_4$), filtered and solvent removed to give a colourless oil (84 mg). The ^1H NMR spectrum of the oil failed to show the presence of the required product.

The synthesis[**149**] *of (S)-4-hydroxymethyl-2-oxazolidinone* (**80**)

Sodium borohydride (72 mg, 1.88 mmol) was added portionwise to solution of oxazolidin-2-one (**39**) (167 mg, 1.15 mmol) in dry ethanol (16 ml) at -3°C. The mixture was warmed to r.t. after the addition and stirred for 4 h. Saturated ammonium chloride solution (8 ml) was added to quench the reaction. The precipitate formed was filtered off and the volume reduced by 33%. The filtrate was left for crystallization at 0°C for 16 h but no solid crystallized out. The solvent was removed to afford the crude product (135 mg) as a white paste in quantitative yield. The ^1H NMR spectrum of the crude (**80**) indicated total reduction of starting material with the absent of impurity. δ_H (270 MHz, D_2O) 4.77 (1H, t, *J* 9, ring CH*H*), 4.50 (1H, dd, *J* 9, 5, ring C*H*H), 4.32-4.22 (1H, m, C*H*), 3.89 (1H, dd, *J* 12, 4, exocyclic CH*H*), 3.79 (1H, dd, *J* 12, 4, exocyclic C*H*H); δ_C (100 MHz, D_2O) 163 (C, O-*C*O-N), 68.7 (CH_2, ring *C*H_2), 63.2 (CH_2, exocyclic *C*H_2), 54.4 (*C*H); ν_{max}/cm^{-1} 3316 (OH), 1734 (O-CO-N).

The formation[**252**] *of methyl (2R,S)-2-amino-3-[(tert-butyldimethylsilyl)oxy] propionate* (**81**)

Imidazole (438 mg, 6.43 mmol) was added to a suspension of (*R,S*)-serine methyl ester hydrochloride (1.00 g, 6.43 mmol) in dichloromethane (5 ml). After 15 min., *tert*-butyldimethylsilyl chloride (1.07 g, 7.10 mmol) was added and the solution was cooled to 0°C. Further portion of imidazole (963 mg, 14.1 mmol) was added to the reaction mixture and then stirred at r.t. for 18 h. An extra equivalent of silylating reagent was added after starting material was detected in the mixture. After the disappearance of starting material, the reaction was quenched with pH 5 water (30 ml). The organic layer was washed with water (4 ml), dried (Na_2SO_4), filtered and solvent removed to give the title compound **(81)** as an oil (1.51 g, 99%). Two vacuum distillations (75-80°C, 0.5 mmHg) were performed on the crude product. The TLC (20% MeOH in EtOAc) of the oil showed the presence of imidazole. After a second workup, the silyl ether **(81)** was obtained in as a pure oil (1.48 g, 6.29 mmol, 98%). δ_H (270 MHz, $CHCl_3$) 3.87 (1H, dd, *J* 10, 4, CH*H*), 3.76 (1H, dd, *J* 10, 4, C*H*H), 3.67 (3H, s, OCH_3), 3.47 (1H, t, *J* 4, C*H*), 1.79 (2H, s, NH_2), 0.82 (9H, s, ^{t}*Bu*), 0.00, 0.01 (3H, s, Si-CH_3); δ_C (100 MHz, $CHCl_3$) 175 (C, CO_2CH_3), 65.5 (CH_2, β-CH_2), 56.7 (CH, α-CH), 52.1 (CH_3, CO_2CH_3), 25.9 (CH_3, ^{t}*Bu*), 18.3 (C, ^{t}*Bu*), -2.77, -3.31 (CH_3, $Si(CH_3)_2{}^t$Bu); m/z (ES+): 234.1 (M-1, 100%), 235.3 (M^+, 10%).

The formation of methyl (2S)-2-amino-3-[(tert-butyldimethylsilyl)oxy] propionate **(81)**

Same procedure as above but with chiral amino acid ester. (*S*)-serine methyl ester hydrochloride (7.65 g, 49.2 mmol), imidazole (11.4 g, 167 mmol), TBDMSiCl (8.66

g, 57.5 mmol) and dichloromethane (50 ml) were used. The crude silyl ether **(81)** was obtained in quantitative yield (12.5 g, 53.1 mmol). TLC indicated residual imidazole as the other impurity.

The formation[**318,152**] *of (1S)-{2-hydroxy-2-methyl-1-[(tert-butyldimethylsilyl)oxy]-propyl}carbamic acid tert-butyl ester* **(82)**

Methyl magnesium bromide (3 M in diethyl ether, 18.4 ml, 55 mmol) was added to a stirred solution of the *O*-protected amino acid ester **(81)** (3.22 g, 13.8 mmol) in diethyl ether (40 ml) under N_2 atmosphere at 0°C. The mixture was stirred at r.t. for 40 h before the solution was adjusted to pH 5 with 2 M hydrochloric acid solution. The organic layer was separated and evaporated to yield an oil (3.33 g) which was purified by flash chromatography (20% MeOH in EtOAc). Two fractions were collected. A larger impure fraction (1 g) and a smaller fraction contained the pure alcohol **(82)** (700 mg, 22%). δ_H (400 MHz, $CHCl_3$) 6.75 (3H, broad s, O*H*, N*H*$_2$), 3.95 (1H, dd, *J* 11, 4, CH*H*), 3.85 (1H, dd, *J* 11, 6, C*H*H), 3.52 (1H, t, *J* 5, α-C*H*), 1.44 (3H, s, C*H*$_3$), 1.35 (3H, s, C*H*$_3$), 0.90 (9H, s, ^{t}*Bu*), 0.14 (3H, s, Si-C*H*$_3$), 0.12 (3H, s, Si-C*H*$_3$); δ_C (100 MHz, $CHCl_3$) 70.8 (C, *C*$(CH_3)_2$), 61.4 (*C*H), 60.2 (CH_2, CH_2O-Si), 28.3 (CH_3, C(*C*$H_3)_2$), 25.9 (CH_3, ^{t}*Bu*), 24.4 (CH_3, C(*C*$H_3)_2$), 18.2 (C, ^{t}*Bu*), -5.3, -5.5 (CH_3, Si(*C*$H_3)_2{}^t$Bu); m/z (ES+): 233.9 (M+, 100%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3376 (broad s, NH_2, OH).

The synthesis of (4R)-4-tert-butyldimethylsilyloxymethyl-5,5-dimethyl-2-oxazolidinone **(83)**

Carbonyldiimidazole (426 mg, 2.63 mmol) was added to a solution of the alcohol **(82)** (534 mg, 2.29 mmol) in dichloromethane (10 ml). The mixture was heated to 40°C under N_2 atmosphere for 16 h before being washed with water (2 x 25 ml). The organic layer was separated and evaporated to give a white solid (550 mg). Purification by column chromatography (40% EtOAc in petroleum ether, 40-60°C) furnished the pure oxazolidin-2-one **(83)** (454 mg, 76%). R_f 0.43 (20% EtOAc in petroleum ether); δ_H (400 MHz, $CHCl_3$) 5.50 (1H, s, N*H*), 3.66 (1H, dd, *J* 10, 6, β-C*H*$_2$), 3.60 (1H, dd, *J* 10, 6, β-C*H*$_2$), 3.54 (1H, t, *J* 6, C*H*), 1.49 (3H, s, C*H*$_3$), 1.38 (3H, s, C*H*$_3$), 0.89 (9H, s, ^{t}*Bu*), 0.07 (6H, s, Si-C*H*$_3$); δ_C (400 MHz, $CHCl_3$) 159 (C, N-*C*O-O), 82.7 (C, O-*C*$(CH_3)_2$-), 62.7 (CH_2, β-*C*H_2), 28.8 (CH_3, O-C(*C*$H_3)_2$), 26.1 (CH_3, ^{t}*Bu*), 21.8 (CH_3, C(*C*$H_3)_2$), 18.5 (C, ^{t}*Bu*); m.p. 95-96°C; m/z (FAB+) 260.1 (M+1, 100%); (Found: C, 55.8; H, 9.6; N, 5.7. $C_{12}H_{24}NO_3Si$ required C, 55.8; H, 9.4; N, 5.4); $[\alpha]_D^{25}$ -36 (*c* = 1 in DCM).

The large scale synthesis[319] *of N-(9-fluorenylmethoxycarbonyl)-(S)-tyrosine methyl ester* **(84)**

9-fluorenylmethyloxycarbonyl-*N*-hydroxysuccinimide (47.5 g, 0.14 mol) in 1,4-dioxane (200 ml) was added portionwise into a stirred solution of (*S*)-tyrosine methyl ester (25.5 g, 0.13 mol) in 1,4-dioxane (90 ml) at 0°C. The reaction mixture was stirred overnight at 0°C with gradual warming to r.t.. The solution was decanted into a mixture of ice/water (1000 ml). A white solid was precipitated out from the aqueous solution. The aqueous layer was splitted into 2 batches. Each batch was

extracted with diethyl ether (3 x 400 ml). The combined diethyl ether layer was reduced in volume, dried (MgSO4), filtered and solvent removed to yield the crude product (46.5 g, 111 mol, 87%) as a yellow oil. The crude material was purified with crystallization from EtOAc/hexane, followed by *t*-butyl methyl ether/hexane system. HPLC analysis of the crystallized material **(84)** to be 95% in purity. δ_H (400 MHz, $CDCl_3$) 7.77 (2 H, d, *J* 7, *Fmoc*), 7.59-7.56 (2 H, m, *Fmoc*), 7.41 (2 H, t, *J* 8, *Fmoc*), 7.32 (2 H, t, *J* 8, *Fmoc*), 6.95 (2 H, d, *J* 9, $C_6\underline{H}_4OH$), 6.75 (2 H, d, *J* 9, $C_6\underline{H}_4OH$), 5.61 (1 H, s, O*H*), 5.31 (1 H, d, *J* 8, N*H*), 4.70-4.60 (1 H, m, α-C<u>H</u>), 4.45 (1 H, dd, *J* 11, 7, CH_2, *Fmoc*), 4.36 (1 H, dd, *J* 11, 7, CH_2, *Fmoc*), 4.22 (1 H, t, *J* 7, CH, *Fmoc*), 3.72 (3 H, s, $OC\underline{H}_3$), 3.06-3.02 (2 H, m, β-$C\underline{H}_2$).

The Mitsunobu coupling of (S)-tyrosine methyl ester with Wang resin using N-methylmorpholine[257]

N-methylmorpholine (10 ml, 0.11 mol) was added to a solution of (*S*)-tyrosine methyl ester hydrochloride **(84)** (507 mg, 2.19 mmol) and Wang resin (0.73 mmol/g, 1g) in dried THF (20 ml). PPh_3 (1 M in THF, 2.19 ml, 2.19 mmol) was added to the mixture. The solution was left to stand at r.t. for 5 min. with periodic agitation. DEAD (345 µl, 2.19 mmol) in THF (2 ml) was added dropwise in 300 µl portion into the mixture with agitation. The solution was agitated for 16 h at r.t.. The resin was filtered and washed with DMA and isopropanol (x 3). The purity of the coupled product was checked by HPLC analysis as described below. The chromatogram indicated a purity of 26%.

General procedure for the coupling of N-Fmoc-(S)-tyrosine methyl ester **(84)** *to Wang resin using Mitsunobu reaction with diisopropylethylamine as base*[258]

Wang resin (1 eq.) was swelled with THF and *N*-Fmoc-(*S*)-tyrosine methyl ester **(84)** (3 eq.) was added, followed by DIPEA (0.1 eq.). PPh_3 (3 eq.) was added and the reaction was cooled to 0°C. Diethyl azodicarboxylate (3 eq.) diluted in dry THF was added slowly dropwise into the solution with agitation. The mixture was agitated for 16 h before the resin was filtered and washed with DMA, then isopropanol. The washing cycle was repeated three times. The resin was dried under vacuum and the weight taken. The purity and substitution level of the resin were determined as detailed below.

Small scale preparation of Wang resin-bound N-Fmoc-(S)-tyrosine methyl ester **(85)**

N-Fmoc-(*S*)-Tyrosine methyl ester **(84)** (914 mg, 2.19 mmol) was coupled to Wang resin (loading capacity 0.73 mmol/g, 1 g) using procedure described above. PPh_3 (1 M in THF, 2.19 ml, 2.19 mmol), DEAD (345 µl, 2.19 mmol) in dry THF (1 ml), DIPEA (40 µl, 0.22 mmol) and THF (10 ml) were used. A substitution level of 50% was obtained. A purity of 71% was detected using HPLC analysis with an UV detector set at 254 nm. *N*-Fmoc-(*S*)-tyrosine methyl ester on Wang resin **(85)** (1.55 g) was obtained after drying. The resin was capped using benzoyl chloride (1 ml), pyridine (1ml) and DMA (10 ml) as described above. The substitution degree was 43% after capping.

Determination of purity of the coupling product

Wang resin-bound *N*-Fmoc-(*S*)-tyrosine **(85)** (50 mg) was suspended in 95% trifluoroacetic acid solution (1 ml). The mixture was agitated for 3 h. The resin was filtered and washed with DCM. The washings were evaporated to leave an oil. The oil was dissolved in MeOH to a concentration of 1 mg/ml and submitted for HPLC analysis. The chromatogram obtained was compared to the known chromatogram of the free *N*-Fmoc-(*S*)-tyrosine methyl ester **(84)**.

Determination of degree of substitution[320]

The substitution degree (mmol/g of Fmoc-tyrosine ester- resin) was determined by the deprotection of a weighed portion of dried *N*-Fmoc-(*S*)-tyrosine methyl ester-resin **(85)** (50 mg) in 20% piperidine in DMA solution (1 ml) for 30 min. The reaction solution (50 µl) was dissolved in MeOH and made up to 25 ml in volume. The absorption of this solution at 300 nm ($\varepsilon = 7800$) caused by the presence of *N*-(9-fluorenylmethyl) piperidine was measured. The coupling yield was calculated by comparing the theoretical weight gained against the experimental weight gained.

General procedure for the capping of unreacted hydroxyl site on the resin-bound N-Fmoc-(S)-tyrosine methyl ester **(85)**

N-Fmoc-(*S*)-tyrosine methyl ester-resin **(85)** (1 eq.) was swelled in DMA. Pyridine (3 eq.) was added followed by benzyl chloride (3 eq.). The reaction mixture was agitated for 24 h. The resin was filtered and washed with DMA, then with isopropanol (x 3). After drying under vacuum, the substitution degree was determined as described above.

Large scale preparation of Wang resin bound N-Fmoc-(S)-tyrosine methyl ester **(85)**

Same procedure as descride above. Wang resin (loading level, 1.16 mmol/g, 5 g) swelled in dried THF (50 ml), *N*-Fmoc-(*S*)-tyrosine methyl ester **(85)** (7.26 g, 17.4 mmol), DIPEA (20% in THF, 1.74 ml), PPh_3 (1 M in THF, 17.4 ml, 17.4 mmol) and DEAD (2.74 ml, 17.4 mmol) in dried THF (7.8 ml) were used. A substitution level of 42% yield was achieved. A weight of 7.80 g was obtained after drying under vacuum. The resin was treated to a 2nd Mitsunobu reaction as described below.

Tandem Mitsunobu coupling reaction of N-Fmoc-(S)-tyrosine methyl ester on Wang resin

N-Fmoc-(*S*)-tyrosine methyl ester **(84)** (7.09 g, 18.7 mmol) was coupled to *N*-Fmoc-(*S*)-tyrosine methyl ester-Wang resin **(85)** (5.33 g, 6.23 mmol, 1.16 mmol g^{-1}) using the same procedure as described above. DIPEA (0.33 ml, 1.87 mmol), PPh_3 (1 M in THF, 18.7 ml, 18.7 mmol) and DEAD (2.95 ml, 18.7 mmol) in dry THF (8.5 ml) were used. After drying, 5.22 g of resin was obtained. The substitution level was measured to be 63%. The resin was capped using benzoyl chloride (3.4 ml) as described previously. Pyridine (3.4 ml) and DMA (50 ml) were also used. The substitution level was 51% after capping. The weight of the capped amino acid bound resin was 5.81 g after drying.

The deprotection of Wang resin-bound N-Fmoc-(S)-tyrosine methyl ester **(85)**

Wang resin-bound *N*-Fmoc-(*S*)-tyrosine methyl ester **(85)** (1.38 g) was dissolved in 20% piperidine in DMA (28 ml) and agitated for 80 min. The resin was filtered,

washed with DMA and isopropanol (x 3), then dried under vacuum. The resin was used in Grignard reaction as described below.

The reaction of Wang resin-bound (S)-tyrosine methyl ester **(87)** *with methyl magnesium bromide*

Dry THF (1 ml x 5) were added to (*S*)-tyrosine methyl ester on Wang resin **(87)** (0.73 mol/g, 100 mg x 5) placed in Reacti vial™ (5 ml) under N_2 atmosphere. The agitated mixture was cooled to 0°C and methyl magnesium bromide (1.4 M in toluene/THF, 10-20 eq.) was added dropwise. The four experiments were kept at 0°C with periodic agitation. After 4 h, one of the reaction was quenched by addition of wet THF (2.5 ml). The resin was filtered and washed with water, then DMA/isopropanol (x 3). The resin was dried to give a net weight of 52 mg. The dried resin was treated with 95% TFA solution (1 ml) and agitated for 3 h before filtration. The resin was washed with DCM (x 4). The filtrate and washings were combined and the solvent was removed to give an oil (27 mg). Three of the other reactions were quenched as before when reaction time was 6, 22 and 72 h. After the usual workup, a yellow oil (6 h: 73 mg; 22 h: 95 mg) were obtained. The last reaction was left standing at 0°C for 72 h, r.t. for 2 d, followed by 2 h at 60°C. The reaction was quenched and worked up in the same manner to give an oil (106 mg). The crude products from all 4 reactions were checked by reverse phase HPLC analysis. See Table 7 & 8 for data.

The formation of (1S)-1-amino-1-(4-benzyloxybenzyl)-2-methylpropan-2-ol **(91)**

Part a: *Using methylamine as desalting reagent*

Methylamine (33% in absolute ethanol) was added to a suspension of *O*-benzyl-(*S*)-tyrosine methyl ester hydrochloride (5.00 g, 15.6 mmol) in ethanol (100 ml) until pH

11 was reached. The solution was filtered and the filtrate was evaporated to give an oil. Dried THF (40 ml) was added to the oil under N_2 atmosphere with stirring. The temp. was cooled to 0°C and methyl magnesium bromide (1.4 M in toluene/THF, 35 ml, 49 mmol) was added slowly to the mixture. The solution was stirred for 16 h at r.t. before a further 1eq of methyl magnesium bromide was added. After 36 h, the reaction was quenched by addition of 1M hydrochloric acid solution until pH 5 was reached. The organic layer was separated and washed with saturated sodium bicarbonate solution. The aqueous layer was adjusted to pH 8 using saturated sodium bicarbonate solution and extracted into dichloromethane (4 x 200 ml). The organic layers were combined, dried (Na_2SO_4), filtered solvent removed to yield a coloured solid (1.42 g). The oil was purified by flash chromatography and eluted with 5% MeOH in DCM. The product **(91)** was obtained in 3% (145 mg, 0.5 mmol). R_f 0.10 (5% MeOH in DCM); δ_H (400 MHz, $CDCl_3$) 7.45-7.31(5H, m, $OCH_2\underline{Ph}$), 7.11 (2H, d, *J* 8, $C_6\underline{H}_4OBn$), 6.95 (2H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.05 (2H, s, $OC\underline{H}_2Ph$), 2.96 (1H, dd, *J* 14, 2, β-$C\underline{H}_2$), 2.76 (1H, dd, *J* 11, 3, α-$C\underline{H}$), 2.22 (1H, dd, *J* 14, 11, β-$C\underline{H}_2$), 1.28 (3H, s, $C\underline{H}_3$), 1.19 (3H, s, $C\underline{H}_3$); δ_C (400 MHz, $CDCl_3$) 157.8 (C, $\underline{C}_6H_4OBn$), 137.5 (C, $OCH_2\underline{Ph}$), 132.4 (C, $\underline{C}_6H_4OBn$), 130.5 (CH, $\underline{C}_6H_4OBn$), 129, 128.4, 127.9 (CH, $OCH_2\underline{Ph}$), 71.8 (C, $\underline{C}(CH_3)_2$), 70.5 (CH_2, $O\underline{C}H_2Ph$), 62 (CH, α-$\underline{C}H$), 38.5 (CH_2, β-CH_2), 27.7, 24.2 ($\underline{C}H_3$). m/z (ES+); 285.9 (M^+, 100%); ν_{max}(DCM)/cm^{-1} ; 3401 (OH), 3018 (ArCH), 1611 (Ar).

Byproducts isolated from the reaction of O-benzyl-(S)-tyrosine methyl ester with methyl magnesium bromide

A pale yellow solid (638 mg) was also recovered from one of the fraction after chromatography. TLC (10% MeOH in DCM) of this solid indicated a mixture of

components. Further purification by column chromatography (6% MeOH in DCM) yielded a white solid which quickly turned yellow in storage. TLC of the solid again revealed a mixture of components. Spectroscopic data collected for this crude sample are listed as follow: $\nu_{max}(CDCl_3)/cm^{-1}$; 3386, 3018, 1661, 1611; m/z (FAB+); 268 (12%), 286 (73%); m/z (CI+) 268 (22%), 286 (100%); m/z (EI+); 266 (37%); m/z (ES+); 268 (5%), 285 (100%); δ_H(400 MHz, $CDCl_3$) 7.47-7.30 (5H, m), 7.25 (1H, m), 7.14 (2H, d, *J* 9), 6.94 (2H, d, *J* 8), 5.05 (2H, s), 3.56 (1H, dd, *J* 9, 4, α-C*H*), 3.20 (1H, dd, *J* 14, 4, β-C*H*$_2$), 2.83 & 2.81 (s, sum = 3H), 2.64 (1H, dd, *J* 14, 9, β-C*H*$_2$), 1.36 (2H, broad s); δ_C (400 MHz, $CDCl_3$) 175 (C), 158 (C), 137 (C), 130.7 (CH), 130.6 (C), 129 (CH), 128.4 (CH), 127.9 (CH), 115.4 (CH), 70.4 (CH_2), 57 (CH), 40.6 (CH_2), 26.2 (CH_3);

Part b: *Using sodium hydrogen carbonate as desalting reagent*

Sodium bicarbonate (1.35 g, 16 mmol) was added to a stirred suspension of hydrochloride salt (5.00 g, 15.6 mmol) in distilled water (230 ml) and dichloromethane (20 ml). After 3 min., the mixture was washed with dichloromethane (2 x 200 ml) and the organic layers were combined, dried (Na_2SO_4), filtered and solvent removed to yield a colourless oil (4.30 g). After drying under vacuum, the oil was dissolved in dry THF (40 ml) under N_2 atmosphere and cooled to -10°C. Methyl magnesium bromide (1.4 M in THF/toluene, 35 ml, 49 mmol) was syringed slowly into the stirred solution over a period of 30 min. After 16 h, an extra 1.5 equivalent of Grignard reagent was added to react with unconsumed starting material as detected by TLC (10% MeOH in DCM). The reaction mixture was stirred for further 20 h at r.t. before quenching with 1 M hydrochloric acid solution. The aqueous layer was adjusted to pH 8 and extracted

with dichloromethane (4 x 200 ml). The organic layers were combined, dried (Na_2SO_4), filtered and solvent removed to yield a coloured solid (7.54 g). The crude mixture was purified by flash chromatography (8% to 20% MeOH in DCM) to afford the pure amino alcohol **(91)** (2.18 g, mmol, 49%). δ_H (400 MHz, $CDCl_3$) 7.47-7.30 (5H, m, $CH_2\underline{Ph}$), 7.12 (2H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.94 (2H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.02 (2H, s, $OC\underline{H}_2Ph$), 2.96 (1H, dd, *J* 13, 2, β-$C\underline{H}_2$), 2.80 (1H, dd, *J* 11, 2, α-C$\underline{H}$), 2.22 (1H, dd, *J* 13, 11, β-$C\underline{H}_2$), 2.18 (1H, br s, O$\underline{H}$), 1.3 (3H, s, $C\underline{H}_3$), 1.2 (3H, s, $C\underline{H}_3$); m/z (ES+) 286.15 (M+1, 89%); δ_C (400 MHz, $CDCl_3$) 157.9 (C, $\underline{C}_6H_4OBn$), 137.4 (C, $OCH_2\underline{Ph}$), 132.5 (C, $\underline{C}_6H_4OBn$), 130.4 (CH, $\underline{C}_6H_4OBn$), 129.0, 128.4, 127.9 (CH, $OCH_2\underline{Ph}$), 115.3 (CH, $\underline{C}_6H_4OBn$), 72.1 (C, $O\underline{C}(CH_3)_2$), 70.4 (CH_2, $O\underline{C}H_2Ph$), 62.3 (CH, α-$\underline{C}H$), 37.3, (CH_2, β-$\underline{C}H_2$), 27.8, 23.9 ($\underline{C}H_3$).

General procedure **[153]** *for the formation of N-t-butyloxycarbonyl-O-benzyl-(S)-tyrosine methyl ester* **(95)**

Thionyl chloride (1.2 ml, 16.2 mmol) was added dropwise to dry methanol (32 ml) at -10° C and the mixture was stirred for 1 h at -10°C. *O*-benzyl-(*S*)-tyrosine (2.19 g, 8.06 mmol) was added portionwise. The mixture was warmed to r.t. and left to stir for 16 h. The solvent was removed to yield the crude *O*-benzyl-(*S*)-tyrosine methyl ester. The crude product was used in the next step without further purification.

A solution of di-*tert*-butyl dicarbonate [$(Boc)_2O$] (1.76 g, 8.07 mmol) in acetone (30 ml) was added dropwise at 0°C to a stirred solution of the crude *O*-benzyl-(*S*)-tyrosine methyl ester and potassium carbonate (1.12 g, 8.07 mmol) in water (25 ml). The solution was stirred for 2 h at r.t. before the acetone was evaporated and replaced by EtOAc (20 ml). The organic layer was separated, dried (Na_2SO_4) and

evaporated to furnish a yellow oil. Purification by flash chromatography (100% EtOAc) yielded the methyl ester **(95)** as a yellow oil (2.79 g, 7.24 mmol, 89%) which solidified on standing. R_f 0.37 (15% EtOAc in petroleum ether); m.p. 57-58°C; δ_H (400 MHz, $CDCl_3$) 7.48-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.05 (2 H, d, *J* 2, $C_6\underline{H}_4OBn$), 6.92 (2 H, d, *J* 2, $C_6\underline{H}_4OBn$), 5.05 (2 H, s, $OC\underline{H}_2Ph$), 4.98 (1H, d, *J* 8, N<u>H</u>), 4.70 (3 H, s, $C\underline{H}_3$), 4.60-4.50 (1H, m, α-C<u>H</u>), 3.10-2.95 (2 H, m, β-$C\underline{H}_2$), 1.43 (9 H, s, *t*-*Bu*); δ_C (400 MHz, $CDCl_3$) 187.4 (C, $\underline{C}O_2$-NH), 172.8 (C, $\underline{C}O_2CH_3$), 158.3 (C, $\underline{C}_6H_4OBn$), 137.4 (C, $OCH_2\underline{Ph}$), 130.7 (CH, $\underline{C}_6H_4OBn$), 129.0 (CH, $OCH_2\underline{Ph}$), 128.6 (C, $\underline{C}_6H_4OBn$), 128.4 (CH, $OCH_2\underline{Ph}$), 127.9 (CH, $OCH_2\underline{Ph}$), 115.3 (CH, $\underline{C}_6H_4OBn$), 80.3 (C, *t*-*Bu*), 70.4 (CH_2, $O\underline{C}H_2Ph$), 54.9 (CH, α-<u>C</u>H), 52.6 (CH_3, $O\underline{C}H_3$), 37.9 (CH_2, β-$\underline{C}H_2$), 28.7 (CH_3, *t*-*Bu*); ν_{max}/cm^{-1} 3433 (CO_2Me), 1745 (CO_2Me), 1715 (O-CO-NH), 1612 (Ar); $[\alpha]_D^{20}$ +41 (*c* = 4.4 in DCM) $[\alpha]_D^{20}$ +39 (*c* = 3.9 in $CHCl_3$).

General procedure for the formation of (1S)-[1-(4-benzyloxybenzyl)-2-hydroxy-2-methylpropyl]carbamic acid tert-butyl ester **(96)**

Methyl magnesium bromide (1.4 M in toluene/THF, 36 ml, 50.4 mmol) was added portionwise to a stirred solution of *N*-Boc-*O*-benzyl-(*S*)-tyrosine methyl ester **(95)** (4.88 g, 12.7 mmol) in dry THF (70 ml) at 0°C under N_2 atmosphere. The solution was warmed to r.t. and stirred for 16 h. Water (10 ml) was added to the mixture and the volume was concentrated under reduced pressure. The residue obtained was redissolved in water (100 ml) and 7 M hydrochloric acid solution was added till the solution reached pH 6. The solution was extracted with EtOAc (2 x 200 ml). The combined organic layer was dried (Na_2SO_4) and the solvent was removed to yield a white solid (4.31 g). Purification by flash chromatography (30% EtOAc in petroleum

ether) afforded the *gem*-dimethyl alcohol **(96)** as a white solid (3.83 g, 9.94 mmol, 79%). R_f 0.30 (30% EtOAc in petroleum ether); m.p. 138-139°C (from EtOAc/ petroleum ether); (Found: C, 71.8; H, 8.2; N, 3.6. $C_{23}H_{31}NO_4$ required C, 71.7; H, 8.1; N, 3.6%); *m/z* (FAB+): 386.2 (M^+, 32%); δ_H (270 MHz, $CDCl_3$) 7.46-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.11 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.90 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.03 (2 H, s, $OC\underline{H}_2Ph$), 4.53 (1 H, d, *J* 9, BocN$\underline{H}$), 3.70-3.50 (1 H, m, α-C$\underline{H}$), 3.02 (1 H, dd, *J* 14, 3, β-C$\underline{H}_2$), 2.60-2.45 (2 H, m, O$\underline{H}$, β-C$\underline{H}_2$), 1.34 [3 H, s, C-(C$\underline{H}_3$)$_2$], 1.28 [3 H, s, C-(C$\underline{H}_3$)$_2$], 1.28 (9 H, s, *t-Bu*); δ_C (400 MHz, $CDCl_3$) 187.4 (C, $\underline{C}O_2$-NH), 157.7 (C), 156.9 (C), 137.5 (C, $OCH_2\underline{Ph}$), 130.4 (CH, $\underline{C}_6H_4OBn$), 129.0 (CH, $OCH_2\underline{Ph}$), 128.3 (CH, $OCH_2\underline{Ph}$), 127.8 (CH, $OCH_2\underline{Ph}$), 115.2 (CH, $\underline{C}_6H_4OBn$), 79.8 (C, *t-Bu*), 73.4 [C, C-(C$\underline{H}_3$)$_2$], 70.4 (CH_2, $O\underline{C}H_2Ph$), 61.0 (CH, α-$\underline{C}$H), 35.5 (CH_2, β-$\underline{C}H_2$), 28.7 (CH_3, *t-Bu*), 28.1 (CH_3, $\underline{C}H_3$), 26.8 (CH_3, $\underline{C}H_3$); ν_{max}/cm^{-1} 1698 (urethane, O-CO-NH); $[\alpha]_D^{20}$ -38 (*c* = 1 in $CHCl_3$).

(1S)-[1-(4-Benzyloxybenzyl)-2-oxopropyl]carbamic acid tert-butyl ester **(97)**

The intermediate ketone **(97)** was also detected in small amount (~ 4%) during purification. R_f 0.21 (15% EtOAc in petroleum ether); m.p. 76-78°C (from EtOAc/ petroleum ether); (Found: C, 71.3; H, 7.4; N, 3.7. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.4; N, 3.8%); δ_H (270 MHz, $CDCl_3$) 7.45-7.32 (5 H, m, $OCH_2\underline{Ph}$), 7.06 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.90 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.15 (1 H, d, *J* 7, BocN$\underline{H}$), 5.02 (2 H, s, $OC\underline{H}_2Ph$), 4.51-4.45 (1 H, m, α-C$\underline{H}$), 3.03 (1 H, dd, *J* 14, 7, β-C$\underline{H}_2$), 2.92 (1 H, dd, *J* 14, 6, β-C$\underline{H}_2$), 2.12 (3 H, s, $COC\underline{H}_3$), 1.41 (9 H, s, *t-Bu*); ν_{max}/cm^{-1} 1708 (ketone, Me-C=O); δ_C (100 MHz, $CDCl_3$) 207.0 (C, $CH_3\underline{C}$=O), 157.8 (C), 136.9 (C, $OCH_2\underline{Ph}$), 130.2 (CH, $\underline{C}_6H_4OBn$), 128.5 (CH, $OCH_2\underline{Ph}$), 128.3 (C, $\underline{C}_6H_4OBn$), 127.7

(CH, $OCH_2\underline{Ph}$), 127.4 (CH, $OCH_2\underline{Ph}$), 114.9 (CH, $\underline{C}_6H_4OBn$), 79.8 (C, *t*-$\underline{Bu}$), 69.9 (CH_2, $O\underline{C}H_2Ph$), 60.7 (CH, α-$\underline{C}H$), 36.6 (CH_2, β-$\underline{C}H_2$), 28.2 (CH_3, *t*-$\underline{Bu}$); $[\alpha]_D^{18}$ +59 (*c* = 1.6 in $CHCl_3$).

The formation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(90)** *using lithium bis(trimethylsilyl)amide*

Lithium bis(trimethylsilyl)amide solution (1 M in THF, 3.84 ml, 3.84 mmol) was added dropwise to a stirring solution of 1,1-dimethyl-2-*N*-*t*-butyloxycarbonyl-3-(*O*-benzyl-4-hydroxyphenyl)-propan-1-ol **(96)** (1.48 g, 3.84 mmol) in dry THF (20 ml) at 0°C under N_2 atmosphere. The mixture was refluxed for 3 h at 68°C before water added and the THF was removed under reduced pressure. Water (30 ml) was added to the yellow residue. The aqueous layer was washed with ethyl acetate (2 x 200 ml). The combined organic layer was dried (Na_2 SO_4), filtered and the solvent removed to give a white solid (1.23 g). The crude product was chromatographed and eluted with 40% EtOAc in hexane to yield the product **(90)** (1.13 g, 3.63 mmol, 94%). R_f 0.37 (40% EtOAc in hexane); m.p. 133-135°C (MeOH); δ_H (270 MHz, $CDCl_3$) 7.45-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.08 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.94 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.05 (2 H, s, $OC\underline{H}_2PH$), 4.88 (1 H, s, N$\underline{H}$), 3.64 (1 H, dd, *J* 11, 4, α-C$\underline{H}$), 2.78 (1 H, dd, *J* 13, 4, β-C$\underline{H}_2$), 2.62 (1 H, dd, *J* 13, 4, β-C$\underline{H}_2$), 1.48 (3 H, s, C$\underline{H}_3$), 1.44 (3 H, s, C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 157.9 (C), 157.8 (C), 136.8 (C, $OCH_2\underline{Ph}$), 129.8 (CH, $\underline{C}_6H_4OBn$), 129.0 (C, $\underline{C}_6H_4OBn$), 128.6 (CH, $OCH_2\underline{Ph}$), 128.0 (CH, $OCH_2\underline{Ph}$), 127.4 (CH, $OCH_2\underline{Ph}$), 115.3 (CH, $\underline{C}_6H_4OBn$), 83.1 [C, $\underline{C}$-$(CH_3)_2$], 70.0 (CH_2, $O\underline{C}H_2Ph$), 63.1 (CH, α-$\underline{C}H$), 36.1 (CH_2, β-$\underline{C}H_2$), 27.5 (CH_3, $\underline{C}H_3$), 21.8 (CH_3,

$\underline{C}H_3$); ν_{max}/cm^{-1} 1750 (urethane, HN-CO-O); (Found: C, 73.2; H, 6.7; N, 4.5. $C_{19}H_{21}NO_3$ required C, 73.3; H, 6.8; N, 4.5%); $[\alpha]_D^{16}$ -85 (*c* = 1 in $CHCl_3$).

The N-acetylation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(90)** *with S(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride*

n-BuLi (1.6 M in hexane, 36 μl, 5.78 x 10^{-5} mol) was added to a stirred solution of auxiliary **(90)** (15 mg, 4.82 x 10^{-5} mol) in dry THF (1 ml) at -78°C under N_2 atmosphere. The reaction mixture was agitated for 30 min. before *S*(+)-MTPACl (11 μl, 5.78 x 10^{-5} mol) was quickly syringed into the solution. The mixture was stirred at -78°C for 1 h and then at r.t. for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 ml) and extracted with EtOAc (4 x 3 ml). The combined extract was dried (Na_2SO_4), filtered and solvent evaporated to give the crude product **(103)**. This crude mixture was dissolved in deuterated $CHCl_3$ and submitted to ^1H NMR analysis. The spectrum showed the presence of starting material and product in a ratio of 17:83. No other peaks were detected. δ_H (270 MHz, $CDCl_3$) 7.60-7.32 (10 H, m, *Ph*), 7.24 (2 H, d, *J* 8, $C_6\underline{H}_4$OBn), 6.94 (2 H, d, *J* 8, $C_6\underline{H}_4$OBn), 5.05 (2 H, s, $OC\underline{H}_2$Ph), 4.63 (1 H, dd, *J* 10, 3, α-C*H*), 3.56 (3 H, s, $OC\underline{H}_3$), 3.17 (1 H, dd, *J* 14, 3, β-$C\underline{H}_2$), 2.89 (1 H, dd, *J* 14, 10, β-$C\underline{H}_2$), 1.30 (3 H, s, $C\underline{H}_3$), 1.20 (3 H, s, $C\underline{H}_3$).

General procedure for the formation (1S)-[1-(4-benzyloxybenzyl)-2-hydroxyethyl] carbamic acid tert-butyl ester **(104)** *using NEPIS/$NaBH_4$ system*[271]

CAUTION: The reductant must be added slowly to prevent excessive foaming. A large reaction vessel must be used to accommodate the increase volume of the reaction mixture during the reduction stage.

N-ethyl-5-phenylisoxazolium-3'-sulphonate (NEPIS) (681 mg, 2.69 mmol) was added to a stirred solution of *N*-Boc-*O*-Benzyl-(*S*)-tyrosine (1.00 g, 2.69 mmol) in dry acetonitrile (24 ml) at r.t. under N_2 atmosphere. White precipitate appeared upon NEPIS addition. The mixture was stirred for 5 min before triethylamine (360 µl, 2.58 mmol) in dried acetonitrile (8 ml) was added dropwise via a pressure equalizing funnel. The solution was stirred for 90 min. during which time the solution turned clear. The solvent was removed to yield a yellow oil which was dissolved in water (26 ml). Sodium borohydride (1.00 g, 26.8 mmol) was added slowly in small portions to the mixture. The reaction mixture was stirred gently for 100 min. before quenching with 1 M hydrochloric acid solution until pH 5 was reached. The solution was extracted with diethyl ether (2 x 250 ml). The washings were dried (Na_2SO_4), filtered and the solvent removed to yield a white solid (1.09 g). Purification with flash chromatography using 35% ethyl acetate in petroleum ether as eluent gave the pure amino alcohol **(104)** (601 mg, 62 %). R_f 0.37 (35% EtOAc in petroleum ether); m.p. 105-107°C; δ_H (400MHz, $CDCl_3$) 7.50-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.14 (2 H, d, *J* 9, $C_6\underline{H_4}OBn$), 6.93 (2 H, d, *J* 9, $C_6\underline{H_4}OBn$), 5.05 (2 H, s, $OC\underline{H_2}Ph$), 4.79 (1 H, d, *J* 8, N$\underline{H}$), 3.38 (1 H, broad s, α-C$\underline{H}$), 3.70- 3.50 (2 H, m, β-C$\underline{H_2}$), 2.79 (2 H, d, *J* 7, $C\underline{H_2}OH$), 2.56 (1 H, s, $CH_2O\underline{H}$), 1.4 (9 H, s, *t-Bu*); δ_C (400 MHz, $CDCl_3$) 157.9 (C), 156.6 (C), 137.4 (C, $OCH_2\underline{Ph}$), 130.8 (CH, $\underline{C}_6H_4OBn$), 129.0 (CH, $OCH_2\underline{Ph}$), 128.4

(CH, $OCH_2\underline{Ph}$), 127.9 (CH, $OCH_2\underline{Ph}$), 115.3 (CH, $\underline{C}_6H_4OBn$), 80.1 (C, *t*-*Bu*), 70.4 (CH_2, $O\underline{C}H_2Ph$), 64.8 (CH_2, $\underline{C}H_2OH$), 54.2 (CH, α-$\underline{C}H$), 36.9 (CH_2, β-$\underline{C}H_2$), 28.8 (CH_3, *t*-*Bu*); ν_{max}/cm^{-1} 3432 (OH), 1705 (urethane, O-C=O-N); (Found: C, 70.7; H, 7.7; N, 3.9. Calc. for $C_{21}H_{37}NO_4$: C, 70.6; H, 7.6; N, 3.9%); $[\alpha]_D^{20}$ -16 (*c* = 1 in $CHCl_3$); literature**[276]** $[\alpha]_D^{18}$ -17 *c* = 6 in $CHCl_3$.

*General procedure***[277]** *for the acylation of (1S)-[1-(4-benzyloxybenzyl)-2-hydroxy-2-methyl-propyl]carbamic acid tert-butyl ester with (+)-camphor-10-sulphonyl chloride*

(+)-Camphor-10-sulphonyl chloride (62 mg, 0.25 mmol) in dry dichloromethane (1 ml) was cannulated into a stirred solution of *N*-Boc amino alcohol **(104)** (80 mg, 0.22 mmol) and pyridine (30 μl, 0.45 mmol) in dried dichloromethane (1.5 ml) under N_2 atmosphere at r.t.. The reaction mixture was agitated for 24 h before partitioned between dichloromethane (10 ml) and aqueous sodium carbonate solution (2 M, 5 ml). The organic layer was washed with water (5 ml), dried (Na_2SO_4), filtered and solvent removed to give a yellow oil (150 mg). The crude mixture was chromatographed and eluted with 20% EtOAc in petroleum ether. Starting material **(104)** (9 mg, 11%), cyclized auxiliary **(105)** (8 mg, 2.82 x 10^{-5} mol, 13%) and sulphonated product **(111)** (87 mg, 0.15 mmol, 68%) were collected. R_f 0.41 (20% EtOAc in petroleum ether); δ_H (400 MHz, $CDCl_3$) 7.43-7.27 (5 H, m, $OCH_2\underline{Ph}$), 7.13 (2 H, d, *J* 8, $C_6\underline{H}_4OBn$), 6.91 (2 H, d, *J* 8, $C_6\underline{H}_4OBn$), 5.02 (2 H, s, $OC\underline{H}_2Ph$), 4.92 (1 H, s, N$\underline{H}$), 4.25 (1 H, broad dd, *J* 9, β-$C\underline{H}_2$), 4.18 (1 H, broad dd, *J* 9, 4, β-$C\underline{H}_2$), 4.10-4.00 (1 H, m, α-CH), 3.59 (1 H, d, *J* 15, camphor-$C\underline{H}_2SO_2$-O), 3.00 (1 H, d, *J* 15, camphor-$C\underline{H}_2SO_2$-O,), 2.90-2.75 (2 H, m, $C\underline{H}_2O$-SO_2-camphor), 2.50-2.34 (2 H,

m, C*H*$_2$, camphor), 2.15-1.90 (4 H, m, C*H*$_2$, camphor), 1.72-1.62 (1 H, m, C*H*, camphor), 1.46 (9 H, s, *t-Bu*), 1.09 (3 H, s, C*H*$_3$, camphor), 0.87 (3 H, s, C*H*$_3$, camphor); δ_C (100 MHz, $CDCl_3$) 214 (C, *C*=O, camphor), 158 (C), 155 (C), 136.9 (C, OCH$_2$*Ph*), 130.2 (CH, *C*$_6$H$_4$OBn), 129.0 (C, *C*$_6$H$_4$OBn), 128.4 (CH, OCH$_2$*Ph*), 127.8 (CH, OCH$_2$*Ph*), 127.3 (CH, OCH$_2$*Ph*), 115.3 (CH, *C*$_6$H$_4$OBn), 79.5 (C, *t-Bu*), 69.8 (CH_2, O*C*H$_2$Ph), 60.2 (CH_2, camphor-*C*H$_2$-SO_2), 57.8 (C, camphor), 50.9 (CH, α-*C*H), 47.9 (C, camphor), 46.8 (CH_2, *C*H$_2$OH), 42.5 (CH, *C*H-camphor), 42.3 (CH_2, *C*H$_2$-camphor), 36.3 (CH_2, β-*C*H$_2$), 28.2 (CH_3, *t-Bu*), 26.7 & 24.7 (CH_2, *C*H$_2$-camphor), 19.5 & 19.4 (CH_3, *C*H$_3$-camphor).

The reaction was repeated with larger quantites of reagents. *N*-Boc-*O*-benzyl-(*S*)-tyrosinol **(104)** (311 mg, 0.87 mmol), pyridine (0.14 ml, 1.74 mmol) and (+)-camphor-10-sulphonyl chloride (240 mg, 0.96 mmol) were used. After workup, the crude material (566 mg) was chromatographed to give a slightly impure product (444 mg, 89%). The sample was purified further to furnish the pure material **(111)** in 78% yield (390 mg, 0.68 mmol).

The formation of (4S)-4-(4-benzyloxybenzyl)-2-oxazolidinone **(105)** *using lithium bis(trimethylsilyl)amide*

Note: The use of aged LiHMDS would impart a yellow colour to the product which required extra purification.

Lithium bis(trimethylsilyl)amide (1 M in THF, 14.3 ml, 14.3 mmol) was syringed into *N*-Boc amino alcohol **(104)** (5.00 g, 14 mmol) in dry THF (80 ml) at 0°C under N_2 atmosphere. The reaction mixture was refluxed at 78°C under N_2 for 4 h. Water (20 ml) was added to the solution before the organic layer was removed. The

mixture was partitioned between EtOAc (150 ml) and water (80 ml). The aqueous layer was further washed with EtOAc (3 x 150 ml). The combined washing was dried (Na_2SO_4), filtered and solvent removed to yield an orange colour solid (3.91 g). The crude product was chromatographed (10% EtOAc in petroleum ether) and crystallized in methanol to give the pure auxiliary **(105)** (3.63 g, 12.8 mmol, 92%). R_f 0.43 (40% EtOAc in petroleum ether); m.p. 135-137°C; δ_H (270MHz, $CDCl_3$) 7.47-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.09 (2 H, d, *J* 9, $C_6\underline{H_4}OBn$), 6.94 (2 H, d, *J* 9, $C_6\underline{H_4}OBn$), 5.41 (1 H, s, N$\underline{H}$), 5.05 (2 H, s, $OC\underline{H_2}Ph$), 4.45 (1 H, t, *J* 8, $C\underline{H_2}O$), 4.14 (1 H, dd, *J* 8, 5, $C\underline{H_2}O$), 4.09-3.98 (1 H, m, α-C$\underline{H}$), 2.80 (2 H, d, *J* 7, β-$C\underline{H_2}$); δ_C (400 MHz, $CDCl_3$) 159.7 (C), 158.4 (C), 137.2 (C, $OCH_2\underline{Ph}$), 130.5 (CH, $\underline{C_6}H_4OBn$), 129.0 (CH, $OCH_2\underline{Ph}$), 128.6 (C, $\underline{C_6}H_4OBn$), 128.5 (CH, $OCH_2\underline{Ph}$), 127.9 (CH, $OCH_2\underline{Ph}$), 115.7 (CH, $\underline{C_6}H_4OBn$), 70.4 (CH_2, $O\underline{C}H_2Ph$), 70.0 (CH_2, $\underline{C}H_2O$), 54.3 (CH, α-$\underline{C}H$), 41.0 (CH_2, β-$\underline{C}H_2$); m/z (ES+): 283.9 (M^+, 100%) (Found: C, 72.1; H, 6.0; N, 4.9. Calc. for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1; N, 4.9%); ν_{max}/cm^{-1} 3453 (HN-C=O), 1754 (urethane, O-C=O-N); $[\alpha]_D^{20}$ -58 (*c* = 0.5 in $CHCl_3$); literature**[278]**: $[\alpha]_D^{18}$ -84.8 *c* = 0.5 in $CDCl_3$.

*General procedure***[321]** *for the O-debenzylation of oxazolidinones*

Palladium on carbon (10%, 0.5 eq. by weight) was added to a solution of the *O*-protected auxiliary in ethanol. The reaction mixture was sparged with hydrogen gas before being placed under H_2 atmosphere and stirred for 16 h. The solution was filtered through celite and the solvent removed to yield the deprotected product.

The formation of (4S)-4-hydroxyphenylmethyl-5,5-dimethyl-2-oxazolidinone **(114)**

The *O*-protected oxazolidinone **(90)** (1.5 g, 4.82 mmol) was deprotected using the procedure as described above. After workup, the product **(114)** was recovered in 97% yield (1.04 g, 4.7 mmol). R_f 0.27 (50% EtOAc in petroleum ether); m.p. 137-139°C; ν_{max}/cm^{-1} 3304 (phenolic group), 1736 (urethane, N-CO-O), 1613 (Ar); δ_H (400 MHz, $CDCl_3$) 8.46 (1 H, s, C_6H_4OH), 6.99 (2 H, d, *J* 9, C_6H_4OH), 6.80 (2 H, d, *J* 9, C_6H_4OH), 5.39 (1H, s, NH), 3.66 (1 H, dd, *J* 10, 5, α-CH), 2.73 (1 H, dd, *J* 14, 5, β-CH_2), 2.56 (1 H, dd, *J* 14, 10, β-CH_2), 1.43 (3 H, s, CH_3), 1.42 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 158.1 (C), 155.9 (C), 129.6 (CH, C_6H_4OBn), 127.2 (C, C_6H_4OBn), 115.3 (CH, C_6H_4OBn), 83.2 [C, C-$(CH_3)_2$], 63.0 (CH, α-CH), 35.9 (CH_2, β-CH_2), 27.3 (CH_3, CH_3), 21.6 (CH_3, CH_3); (Found: C, 64.9; H, 6.8; N, 6.3. $C_{12}H_{15}NO_3$ required C, 65.4; H, 6.8; N, 6.3%); $[\alpha]_D^{18}$ -76 (*c* = 1 in MeOH).

General procedure for the formation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)**

n-BuLi (1.6 M in hexane, 11.9 ml, 19.1 mmol) was added portionwise into a cooled solution of auxiliary **(90)** (5.16 g, 16.6 mmol) in dry THF (40 ml) at -78°C with stirring and under N_2 atmosphere. After 15 min., propionyl chloride (1.93 ml, 21.6 mmol) was syringed slowly into the solution and agitated for 35 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 ml) and extracted with EtOAc (3 x 100 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent removed to give a pale yellowish white solid (6.50 g). The crude product was purified by repeated crystallization in methanol (x 2) to furnish the pure product **(123)** (5.67 g, 15.4 mmol, 93%). The methanol removed the acid chloride impurity

by forming the ester. This was evident by the white fume given off in dissolution and the removal of the yellow colour. R_f 0.42 (20% EtOAc in hexane); m.p. 124-125°C (MeOH); ν_{max}/cm^{-1} 1770 (urethane, N-CO-O), 1700 (EtCO-N); δ_H (270 MHz, $CDCl_3$) 7.50-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.18 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.91 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.04 (2 H, s, $OC\underline{H}_2Ph$), 4.44 (1 H, dd, *J* 10, 4, α-C$\underline{H}$), 3.06 (1 H, dd, *J* 14, 4, β-C$\underline{H}_2$), 3.00-2.77 (3 H, m, CH_3CH_2CO, β-C$\underline{H}_2$), 1.38 (3 H, s, C$\underline{H}_3$), 1.35 (3 H, s, C$\underline{H}_3$), 1.14 (3 H, t, *J* 8, $C\underline{H}_3CH_2CO$); δ_C (100 MHz, $CDCl_3$) 174.2 (C, Et$\underline{C}$O-N), 157.6 (C), 152.6 (C), 136.9 (C, $OCH_2\underline{Ph}$), 130.0 (CH, $\underline{C}_6H_4OBn$), 129.2 (C, $\underline{C}_6H_4OBn$), 128.5 (CH, $OCH_2\underline{Ph}$), 127.9 (CH, $OCH_2\underline{Ph}$), 127.4 (CH, $OCH_2\underline{Ph}$), 114.9 (CH, $\underline{C}_6H_4OBn$), 82.1 [C, $\underline{C}$-$(CH_3)_2$], 70.0 ($O\underline{C}H_2$ Ph), 63.6 (CH, α-$\underline{C}$H), 34.4 (CH_2, β-$\underline{C}H_2$), 29.3 (CH_2, $CH_3\underline{C}H_2$ C=O), 28.6 (CH_3, $\underline{C}H_3$), 22.2 (CH_3, $\underline{C}H_3$), 8.33 (CH_3, CH_3CH_2C=O); (Found: C, 71.8; H, 6.9; N, 3.8. $C_{22}H_{25}NO_4$ required C, 71.9; H, 6.9; N, 3.8%); $[\alpha]_D^{20}$ -28 (*c* = 1 in DCM).

The formation of (4S)-4-(4-hydroxyphenylmethyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidin-2-one **(143)** *for the purpose of FTIR data collection and analysis for solid phase N-propionylation reaction*

The *O*-benzyl protected *N*-acyloxazolidinone **(123)** (2.31 g, 6.29 mmol) was deprotected using the method as described previously. An unoptimised yield of **(143)** in 61% (1.06 g, 3.82 mmol) was obtained after workup. R_f 0.57 (40% EtOAc in petroleum ether); m.p. 127-129°C; ν_{max}/cm^{-1} 3407 (phenolic group), 1774 (urethane, N-CO-O), 1703 (EtC=O), 1613 (Ar); (Found: C, 65.1; H, 7.0; N, 5.1. $C_{15}H_{19}NO_4$ required C, 65.0; H, 7.0; N, 5.1%); *m/z* (FAB+): 278.2 (MH^+, 100%); δ_H

(400 MHz, $CDCl_3$) 7.11 (2 H, d, *J* 8, $C_6\underline{H}_4OH$), 6.77 (2 H, d, *J* 8, $C_6\underline{H}_4OH$), 5.79 (1H, s, O*H*), 4.45 (1 H, dd, *J* 9, 4, α-C*H*), 3.02 (1 H, dd, *J* 14, 4, β-C$\underline{H}_2$), 2.93 (2 H, q, *J* 7, $CH_3C\underline{H}_2$ C=O), 2.84 (1 H, dd, *J* 14, 9, β-C$\underline{H}_2$), 1.40 (3 H, s, C$\underline{H}_3$), 1.37 (3 H, s, C$\underline{H}_3$), 1.15 (3 H, t, *J* 8, C$\underline{H}_3CH_2$C=O); δ_C (100 MHz, $CDCl_3$) 174.7 (C, Et$\underline{C}$=O), 154.7 (C), 152.9 (C), 130.2 (CH, $\underline{C}_6H_4OBn$), 128.6 (C, $\underline{C}_6H_4OBn$), 115.6 (CH, $\underline{C}_6H_4OBn$), 82.5 [C, $\underline{C}$-$(CH_3)_2$], 63.7 (CH, α-$\underline{C}$H), 34.5 (CH_2, β-$\underline{C}H_2$), 29.4 [CH_2, $CH_3\underline{C}H_2C$=O], 28.6 (CH_3, $\underline{C}H_3$), 22.2 (CH_3, $\underline{C}H_3$), 8.41 [CH_3, $\underline{C}H_3CH_2C$=O]; $[\alpha]_D^{20}$ -34.5 (*c* = 1.1 in DCM) $[\alpha]_D^{18}$ -25 (*c* = 4 in MeOH).

Small scale coupling of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(114)** *to Merrifield resins*[280]

Potassium hydride (86 mg, 0.75 mmol) was added portionwise to a stirred solution of oxzaolidinone **(114)** (111 mg, 0.50 mmol) in DMF (4 ml) at 0°C under N_2 atmosphere. After 2 h of stirring, this mixture was cannulated into a suspension of Merrifield resins (500 mg, 0.6-1.0 mmol/g) swollened in DMF (4 ml) and 18-crown-6 (53 mg, 0.20 mmol). The reaction mixture was heated to 80°C for 5 d with periodic agitation. The TLC (50% EtOAc in petroleum ether) of the mixture indicated consumption of the auxiliary after 2 d. The resins were filtered and washed with DMF (40 ml), MeOH (40 ml), THF (40 ml) and Et_2O (40 ml). The yellow coloured resins were dried under vacuum to constant weight (538 mg). FTIR spectrum of the crushed resins in KBr disc revealed peak at 1750 cm^{-1} (urethane, C=O) compared with the original Merrifield resins. The yield was calculated based on weight gained.

Theoretical weight of resin-bound auxiliary: 500 + 111 - (0.5 mmol x 36.5) = 593 mg		
Theoretical weight gained: 93 mg	Actual weight gained: 38 mg	Coupling yield: 38/93 = 41%

New loading value: 500/538 x 1 = 0.93 mmol g^{-1}

Tandem coupling of coupling of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(114)** *to Merrifield resins*

Same procedure as above. Oxazolidinone **(114)** (634 mg, 2.87 mmol, 1.4 eq.), Merrifield resins (2 g, 1 mmol g^{-1}), 18-crown-6 (0.4 eq.), potassium hydride (2 eq.) and DMF (50 ml) were used for the first coupling reaction. Dried resin-bound auxiliary (2.25 g) was obtained. Small amount of the product (400 mg) was used in small scale *N*-propionylation test without capping the unreacted sites.

Theoretical yield: 2 + (2 mmol x 221.24) - (2 mmol x 36.5) = 2.37 g		
Theoretical weight gained: 370 mg	Actual weight gained: 250 mg	Coupling yield: 250/370 = 68%

New loading value: (2/2.25) x 1 = 0.89 mmol g^{-1}

The resin-bound auxiliary **(121)** (1.74 g, 1.55 mmol) was subjected to a 2nd coupling reaction. The conditions remained unchanged. Oxazolidinone **(114)** (1.3 eq.) was used. The resin-bound auxiliary **(121)** was dried to give a weight of 1.77 g. The FTIR spectrum of the crushed resins had a more prominent carbonyl peak at 1749 cm^{-1} and C=C double bond at 1602 cm^{-1}.

Theoretical yield: 1.74 + (1.55 mmol x 221.24)-(1.55 mmol x 36.5) = 2.03 g		
Theoretical weight gained: 290 mg	Actual weight gained: 34 mg	Coupling yield: 34/290 = 12%

New loading value: (1.74/1.77) x 0.89 = 0.87 mmol g^{-1}

This batch of resin-bound auxiliary was capped using the method as described below.

The N-propionylation of uncapped resin-bound auxiliary

Part a: *Using n-BuLi and propionyl chloride*

n-BuLi (1.6 M in hexane, 250 μl, 0.40 mmol) was added slowly to a suspension of resin-bound auxiliary **(121)** (400 mg, 0.36 mmol) in dry THF (6 ml) at -78°C under N_2 atmosphere. The suspension was agitated for 10 min. before propionyl chloride (0.32 ml, 3.68 mmol) was added. After 90 min., the resins were filtered and washed with THF, Et_2O, MeOH and THF (2 x 40 ml). A weight of 415 mg was obtained after drying the resins under vacuum. FTIR anaysis of the crushed beads did not indicate acylation. The resins (370 mg, 0.33 mmol) were capped using the method as described below. A weight of 316 mg of resins were recovered. (Theoretical weight: 369 mg). This batch of capped resins were treated with DMAP/Et_3N/propionyl anhydride twice using conditions as described below. FTIR spectrum of the crushed resins showed a small peak at 1672 cm^{-1} which could be caused by the *N*-propionylated product. Subsequent removal of the auxiliary derivative using Pd(II) catalyst and H_2 gas system failed to yield any detectable product.

Part b: *Using DMAP/Et_3N/propionyl chloride*

Triethylamine (97 μl, 0.70 mmol) was added to a mixture of DMAP (11 mg) and resin-bound auxiliary **(121)** (480 mg, 0.45 mmol) swollened in dry THF (10 ml) under N_2 atmosphere. Propionyl chloride (80 μl, 0.92 mmol) was added dropwise into the solution and the mixture was agitated periodically for 30 min. before

refluxing for 4 d. The resins were filtered and washed with solvents as before. The resins were dried to give a weight of 440 mg. FTIR analysis of the crushed beads indicated no reaction.

The capping[38] *of unreacted sites on resin bound auxiliary*

Sodium iodide (1.45 g, 9.68 mmol) was added to the resin-bound auxiliary **(121)** (1.39 g, 1.21 mmol) swollen in acetone (8 ml). The reaction mixture was refluxed for 2 d before the resins were filtered, washed and dried as before. Dry THF (8 ml) was used to swollen the resin and tributyltin hydride (0.65 ml, 2.42 mmol) was added. The mixture was refluxed for 2 d. The capped resins were washed with THF (2 x 50 ml), EtOH (2 x 50 ml), MeOH (2 x 50 ml) and Et_2O (2 x 50 ml). After drying, a weight of 1.36 g was obtained. The FTIR spectrum of the crushed resins showed an increased absorbance of the C-H stretch at around the 3000 cm^{-1} region. The carbonyl stretch was clearly visible at 1746 cm^{-1}.

Theoretical weight: 1.39 - [1.21 mmol x (35.5-1.0)] = 1.35 g	
Theoretical loading level: 0.87 x 1.39/1.35 = 0.90 mmol g^{-1}	
Theoretical weight loss: 40 mg	Actual weight loss: 30 mg

Actual loading level: 0.87 x 1.39/1.36 = 0.89 mmol g^{-1}

The capped resins were subjected to *N*-propionylation as described below.

The N-propionylation of capped resin-bound auxiliary **(121)** *with n-BuLi and propionyl anhydride*

n-BuLi (1.6 M in hexane, 73 μl, 0.12 mmol) was added to capped resin-bound auxiliary **(121)** (100 mg, 8.90 x 10^{-5} mol) swollen in dry THF (2 ml) at -78°C

under N_2 atmosphere. After 20 min. of periodic agitation, propionyl anhydride (114 µl, 0.89 mmol) was added and the mixture was kept at -78°C for 30 min., then at r.t. for 30 min. The resins were filtered and washed with usual solvents and dried. The FTIR spectrum did not indicated the presence of propionylated product.

The N-propionylation of capped resin-bound oxazolidin-2-one **(121)** *with DMAP/Et_3N/propionyl anhydride*

Capped resin-bound auxiliary **(121)** (1.36 g, 1.21 mmol) was swollened in THF (8 ml) containing DMAP (15 mg, 0.12 mmol) and Et_3N (0.34 ml, 2.44 mmol) under N_2 atmosphere. Propionic anhydride (0.47 ml, 3.67 mmol) was added and the reaction mixture was refluxed for 4 d. The resins were filtered and washed with DMF (2 x 40 ml), MeOH (2 x 40 ml), THF (2 x 40 ml) and Et_2O (2 x 40 ml). The resins were dried to give a weight of 1.35 g before being subjected to a 2nd, 3rd and 4th coupling reaction. FTIR analysis indicated no reaction. An attempted cleavage of the resins (1.02 g) with H_2 gas and palladium(II) acetate as described below.

The attempted cleaving of resin-bound oxazolidin-2-one **(121)** *with hydrogenation*[283]

Palladium acetate (90 mg, 0.39 mmol) was added to capped resin-bound auxiliary **(121)** (200 mg, 0.18 mmol) suspended in DCM (8 ml). The atmoshpere was replaced by H_2 gas and stirred for 24 h. The colour of the catalyst changed from orange to black. The reaction mixture was filtered with celite and washed with DCM (2 x 50 ml). The combined organic layers was washed with 2 M $NaHCO_3$ solution (75 ml), water (50 ml), brine (50 ml), dried (Na_2SO_4) and filtered. The

solvent was removed to yield an oil which was submitted to ^{1}H NMR analysis. The ^{1}H NMR spectrum detected only the presence of cleaved non-propionylated auxiliary **(114)**, as evident by the NH signal which resonated at δ5.30. This compared with δ5.39 taken from the NMR spectrum of the authentic sample.

The formation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-[(2R)-2-benzyl-1-oxopropyl]-2-oxazolidinone **(124)** *at low reaction temperature*[322]

Part a: *Under standard conditions*

n-BuLi (1.6 M in hexane, 0.94 ml, 1.50 mmol) was transferred to a stirred solution of diisopropylamine (0.23 ml, 1.63 mmol) in dry THF (2 ml) at 0°C under N_2 atmosphere. After 40 min., the temperature was cooled to -78°C and *N*-acylated auxiliary **(123)** (500 mg, 1.36 mmol) in dry THF (4 ml) was added. Benzyl bromide (0.33 ml, 2.72 mmol) was added to the enolate solution after 30 min. The solution was stirred at -78°C for 1 h before being kept at 0°C for 3 h. TLC (20% EtOAc in petroleum ether) of the reaction mixture indicated the presence of product as well as starting material. The solution was warmed to r.t. and left stirring for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with dichloromethane (4 x 10 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent removed to yield a yellow oil (902 mg). Purification with column chromatography (5% to 40% EtOAc in petroleum ether) furnished the α-benzylated product **(124)** (172 mg, 0.38 mmol, 28%). R_f 0.48 (10% EtOAc in petroleum ether); m.p. 80-82°C (EtOAc/petroleum ether); (Found: C, 75.8; H, 6.8; N, 3.0. $C_{29}H_{31}NO_4$ required C, 76.1; H, 6.8; N, 3.1%); ν_{max}/cm^{-1} 3430 (C-C=O-N), 1772 (urethane, N-CO-O), 1696 [$CH_3CH(Bn)C=O$], 1609 (Ar); *m/z* (FAB+) 458.2 (MH^+,

64%); δ_H (270 MHz, $CDCl_3$) 7.45-7.20 (10 H, m, $OCH_2\underline{Ph}$, $CH_2\underline{Ph}$), 7.12 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.88 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.01 (2 H, s, $OC\underline{H}_2Ph$), 4.41 (1 H, dd, *J* 10, 3, α-C*H*), 4.12 [1 H, m, $CH_3C\underline{H}(Bn)C{=}O$], 3.08 (1 H, dd, *J* 13, 6, $CH_3CHC\underline{H}_2PhC{=}O$), 2.88 (1 H, dd, *J* 14, 3, β-$C\underline{H}_2$), 2.70-2.50 (2 H, m, β-$C\underline{H}_2$, $CH_3CHC\underline{H}_2$ $PhC{=}O$), 1.30 (3 H, s, $C\underline{H}_3$), 1.29 (3 H, s, $C\underline{H}_3$), 1.15 (3 H, d, *J* 7, $C\underline{H}_3CHCH_2PhC{=}O$); δ_C (100 MHz, $CDCl_3$) 176.9 (C, $CH_3CH(Bn)\underline{C}O\text{-}N$), 157.5 (C), 152.3 (C), 114.9 (CH, $\underline{C}_6H_4OBn$), 81.8 [C, *C*-$(CH_3)_2$], 69.9 ($O\underline{C}H_2Ph$), 63.7 (CH, α-*C*H), 39.9 [CH_2, $CH_3CH(\underline{Bn})C{=}O$], 39.5 [CH, $CH_3\underline{C}H(Bn)C{=}O$], 33.9 ($CH_2$, β-$\underline{C}H_2$), 28.5 [$CH_3$, C-$(\underline{C}H_3)_2$], 22.2 [$CH_3$, C-$(\underline{C}H_3)_2$], 16.4 [$CH_3$, $\underline{C}H_3CH(Bn)C{=}O$].

The depropionylated oxazolidin-2-one **(90)** (142 mg, 0.46 mmol, 34%) and (4*S*)-3-benzyl-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(125)** (105 mg, 0.26 mmol, 19%) were collected as the other two major side products.

(4S)-3-Benzyl-4-(4-benzyloxybenzyl)-5,5-dimethyl-2-oxazolidinone **(125)**

R_f 0.35 (20% EtOAc in petroleum ether); ν_{max}/cm^{-1} 1737 (urethane, N-CO-O), 1610 (Ar); δ_H (270 MHz, $CDCl_3$) 7.60-7.06 (10 H, m, $\underline{Ph}CH_2$-N, $\underline{Ph}CH_2O$), 6.95 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.88 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.04 (2 H, s, $OC\underline{H}_2Ph$), 4.78 (1 H, d, *J* 15, $PhC\underline{H}_2$ -N), 3.83 (1 H, d, *J* 15, $PhC\underline{H}_2$ -N), 3.47 (1 H, dd, *J* 8, 6, α-C*H*), 2.94 (1 H, dd, *J* 14, 6, β-$C\underline{H}_2$), 2.65 (1 H, dd, *J* 14, 8, β-$C\underline{H}_2$), 1.35 (3 H, s, $C\underline{H}_3$), 1.07 (3 H, s, $C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 157.7 (C), 157.6 (C), 136.7 (C, $OCH_2\underline{Ph}$), 136.0 (C, $\underline{Ph}CH_2$ N), 129.8 (CH, $\underline{C}_6H_4OBn$), 128.8 (C, $\underline{C}_6H_4OBn$), 128.6 (CH, $OCH_2\underline{Ph}$), 128.5 (CH, $\underline{Ph}CH_2$ N), 128.1 (CH, $\underline{Ph}CH_2$ N), 127.9 (CH, $OCH_2\underline{Ph}$), 127.7 (CH, $\underline{Ph}CH_2$ N), 127.4 (CH, $OCH_2\underline{Ph}$), 115.1 (CH, $\underline{C}_6H_4OBn$), 80.9 [C, $\underline{C}$-$(CH_3)_2$], 69.9 (CH_2, $O\underline{C}H_2Ph$), 64.1 (CH, α-*C*H), 46.4 (CH_2, $Ph\underline{C}H_2$ N), 34.1 (CH_2, β-$\underline{C}H_2$), 27.7 (CH_3,

$\underline{C}H_3$), 22.1 (CH_3, $\underline{C}H_3$); m.p. 94-95°C (MeOH); m/z (FAB+ acc. mass): Found M^+, 402.20644; $C_{26}H_{27}NO_3$ required 402.20691); $[\alpha]_D^{20}$ -16.5 ($c = 2$ in $CHCl_3$).

Part b: *With alkylation at -78°C for 3 h then r.t. for 16 h*

Same procedure as Part a) but the reaction was carried out on 120 mg scale. The enolate formation stage took 30 min. at -78°C. The enolates were allowed to react with benzyl bromide at -78°C for 3 h before warming to r.t. and stirred for 16 h. The reaction was quenched using saturated aqueous NH_4Cl (2 ml). TLC (20% EtOAc on petroleum ether) of the reaction mixture at the end of the 3 h showed the presence of product and large amount of unreacted auxiliary. After 16 h, no starting auxiliary could be detected. Only the alkylated product **(124)**, *N*-benzylated auxiliary **(125)** and the deacylated auxiliary **(90)** were detected.

Part c: *With alkylation at -78°C for 40 min, 0°C for 3 h*

Same procedure as Part a) except the reaction was carried out on 100 mg scale. The enolate formation stage took 40 min. at -78°C. The alkylation occurred at -78°C for 40 min., followed by 3 h at 0°C and 20 min. at r.t. before quenching. TLC of the reaction mixture after 3 h at 0°C showed the presence of product **(124)**, starting material and the two side products. Warming at r.t. for 20 min. did not improved the conversion any further. A yield of 17% was obtained for the product **(124)**. Starting material **(121)** (50%) was also recovered.

Part d: *With alkylation at -78°C for 30 min, -10°C for 1 h and -5°C for 2 h*

Same procedure as Part a) except the reaction was carried out on a 100 mg scale. The enolate formation stage took 30 min. at -78°C. The alkylation occurred at -78°C for 30 min., followed by -10°C for 1 h and -5°C for 2 h before quenching. TLC of

the reaction mixture after quenching indicated a mixture of product **(124)**, starting material **(123)** (less than Part c) and side products.

The formation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-[(2R)-2-benzyl-1-oxopropyl]-2-oxazolidinone **(124)** *at 0°C* **[284]**

LDA (1.5 M in hexane, 0.60 ml, 0.90 mmol) was added to a stirred solution of *N*-propionyloxazolidinone **(123)** (300 mg, 0.82 mmol) in dry THF (3 ml) at 0°C under N_2 atmosphere. The solution was stirred at 0°C for 30 min. before benzyl bromide (0.49 ml, 4.12 mmol) was added. The mixture was stirred at 0°C for 30 min. followed by 50 min. at r.t. before quenching with saturated aqueous NH_4Cl (2 ml). The separated aqueous layer was extracted with DCM (3 x 15 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent evaporated to give a yellow oil (1.18 g). Purification with chromatography (10 % EtOAc in petroleum ether) furnished the product **(124)** as a white solid (176 mg, 0.38 mmol, 47%). $[\alpha]_D^{20}$ -58 (*c* = 1.7 in DCM); $[\alpha]_D^{20}$ -65 (*c* = 4 in $CHCl_3$); R_f 0.28 (10% EtOAc in petroleum ether). The auxiliary **(90)** was recovered in 94% yield while the α-alkylated acid **(136)** was collected in 76% yield. The recovery rate was improved to >98% for both compounds in repeat experiments. The benzylated acid was recovered using the conditions described below.

(*R*)-2-Methyl-3-phenylpropionic acid **(136)**: R_f 0.29 (20% EtOAc in petroleum ether); $[\alpha]_D^{18}$ -31.8 (*c* = 1.7 in DCM); lit**[285]**: $[\alpha]_D^{22}$ -31.1 (*c* = 1.03 in DCM); δ_H (270 MHz, $CDCl_3$) 7.35-7.15 (5 H, m, *Ph*), 3.08 (1 H, dd, *J* 13, 6, β-C*H*$_2$), 2.85-2.70 (1 H, m, α-C*H*), 2.66 (1 H, dd, *J* 13, 8, β-C*H*$_2$), 1.18 (3 H, d, *J* 7, C*H*$_3$); δ_C (100

MHz, $CDCl_3$) 182.5 (C, $\underline{C}O_2H$), 139.0 (C, *Ph*), 129.0, 128.4, 126.4 (CH, *Ph*), 41.2 (CH, α-$\underline{C}H$), 39.3 (CH_2, β-$\underline{C}H_2$), 16.5 (CH_3, $\underline{C}H_3$).

General procedure **[231]** *for the recovery of α-alkylated propionic acid and oxazolidin-2-ones*

Alkylated *N*-propionyloxazolidin-2-one (1 eq.) was dissolved in a mixture of THF/water (3:1) and cooled to 0°C. Aqueous hydrogen peroxide (27.5%, 4.8 eq.) followed by lithium hydroxide (2 eq.) were added to the cooled solution. The reaction mixture was agitated at 0°C and quenched with aqueous 1 M Na_2SO_3 solution when TLC (25% EtOAc in petroleum ether) indicated complete reaction. The organic solvent was removed under reduced pressure. The remaining aqueous layer was extracted with dichloromethane (x 3). The combined organic layer was dried (Na_2SO_4), filtered and solvent removed to yield the recovered auxiliary.

The aqueous layer was acidified to pH 1 with aqueous 2 M hydrochloric acid solution. The solution turned cloudy upon acidification. The aqueous layer was washed with EtOAc (x 3). The combined washing was dried ($MgSO_4$), filtered and solvent removed to yield the α-alkylated propionic acid.

General procedure for the formation of (1S)-[1-(4-benzyloxybenzyl)-2-hydroxy-ethyl] carbamic acid tert-butyl ester **(104)** *using isopropyl chloroformate/$NaBH_4$ system*

CAUTION: The reductant must be added slowly as this reduction is an exothermic reaction.

Isopropyl chloroformate (1 M solution in toluene, 2.7 ml, 2.70 mmol) was added to a stirred solution of *N*-Boc-*O*-Benzyl-(*S*)-tyrosine (1.00 g, 2.69 mmol) and triethylamine (0.80 ml, 2.73 mmol) in dry THF (15 ml) at -5°C under N_2 atmosphere. The mixture was stirred for 90 min. at -5°C before the solvent was removed *in vacuo* to yield a yellow oil which was redissolved in water (30 ml). Sodium borohydride (1.02 g, 26.9 mmol) was added slowly in small portions to the mixture over 20 min. and then stirred gently for 165 min. at r.t.. The reaction mixture was quenched with 1 M hydrochloric acid solution until pH 5 was reached. The aqueous layer was extracted with diethyl ether (3 x 100 ml). The organic layers were combined, dried (Na_2SO_4) and filtered. The solvent removed to yield an yellow oil (1.78 g). Purification with flash chromatography using 30% ethyl acetate in petroleum ether as eluent gave the pure product **(104)** (609 mg, 1.70 mmol, 63%); $[\alpha]_D^{20}$ -16 (c = 1 in DCM); Lit**[276]**: $[\alpha]_D^{18}$ -17 c = 6 in $CDCl_3$). Spectroscopic data obtained are in agreement with the data derived from the NEPIS/$NaBH_4$ method.

The formation of (4S)-4-(4-benzyloxybenzyl)-2-oxazolidinone **(105)**

The product **(105)** was formed in 92% yield using the same procedure as described earlier. All spectroscopic data matched those data obtained from the NEPIS/$NaBH_4$ method. $[\alpha]_D^{20}$ -58 (c = 0.53 in $CHCl_3$) lit**[278]** : $[\alpha]_D^{18}$ -84.8 c = 0.5 in $CDCl_3$).

General procedure for the formation of (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone **(130)**

n-BuLi (2.5 M in hexane, 4.92 ml, 12.3 mmol) was added portionwise into a cooled solution of auxiliary **(105)** (3.47 g, 12.2 mmol) in dry THF (30 ml) at -78°C with stirring and under N_2 atmosphere. After 15 min., propionyl chloride (1.28 ml, 14.7 mmol) was syringed slowly into the solution and agitated for 35 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with EtOAc (5 x 40 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent removed to give a pale yellowish white solid (4.10 g). Pure product **(130)** (3.83 g, 11.2 mmol, 92%) was obtained after repeated crystallization from methanol. R_f 0.37 (20% EtOAc in petroleum ether); m.p. 92-94°C; (Found: C, 70.6; H, 6.3; N, 4.1. Calc. for $C_{20}H_{21}NO_4$: C, 70.8; H, 6.2; N, 4.1%); ν_{max}/cm^{-1} 1780 (urethane, N-CO-O), 1704 (EtC=O-N), 1611 (Ar); δ_H (400MHz, $CDCl_3$) 7.45-7.30 (5 H, m, $OCH_2\underline{Ph}$), 7.11 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.93 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.04 (2 H, s, $OC\underline{H}_2Ph$), 4.64-4.58 (1 H, m, α-C$\underline{H}$), 4.22-4.13 (2 H, m, $C\underline{H}_2O$), 3.21 (1 H, dd, *J* 14, 3, β-$C\underline{H}_2$), 3.04-2.86 (2 H, m, $CH_3C\underline{H}_2C$=O), 2.72 (1 H, dd, *J* 14, 9, β-$C\underline{H}_2$), 1.19 (3 H, t, *J* 7, $C\underline{H}_3CH_2C$=O); δ_C (100MHz, $CDCl_3$) 174 (C, Et$\underline{C}$=O-N), 158.1 (C), 153.5 (C), 136.8 (C, $OCH_2\underline{Ph}$), 130.5 (CH, $OCH_2\underline{Ph}$), 128.6 (CH, $OCH_2\underline{Ph}$), 128 (CH, $OCH_2\underline{Ph}$), 127.5 (CH, $OCH_2\underline{Ph}$), 115.3 (CH, $\underline{C}_6H_4OBn$), 70.0 (CH_2, $O\underline{C}H_2Ph$), 66.2 (CH_2, $\underline{C}H_2O$), 55.2 (CH, α-$\underline{C}$H), 37.0 (CH_2, β-$\underline{C}H_2$), 29.2 (CH_2, $CH_3\underline{C}H_2C$=O), 8.30 (CH_3, $\underline{C}H_3CH_2C$=O); $[\alpha]_D^{20}$ +69 (*c* = 1 in DCM) $[\alpha]_D^{20}$ +54 (*c* = 1 in $CHCl_3$).

The experiment was repeated with a diffferent amount of oxazolidinone **(105)** (1.84 g, 6.49 mmol). After workup, the crude sample was chromatographed and eluted

with 20% EtOAc in petroleum ether to afford the pure product **(130)** in yield of 97% (2.14 g, 6.31 mmol).

The formation of (4S)-4-(4-benzyloxybenzyl)-3-[(2R)-2-benzyl-1-oxopropyl]-2-oxazolidinone **(139)** *at 0°C*

LDA (2 M in THF/heptane, 380 μl, 0.76 mmol) was added to a stirred solution of the *N*-propionylated auxiliary **(130)** (250 mg, 0.74 mmol) in dry THF (2.5 ml) at 0°C under N_2 atmosphere. After 30 min., benzyl bromide (0.44 ml, 3.70 mmol) was added. The solution was agitated for 30 min. before warming to r.t. and stirred for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 ml) and partitioned between DCM (15 ml) and water (5 ml). The aqueous layer was further extracted with DCM (2 x 15 ml). The organic layer was dried (Na_2SO_4), filtered and solvent removed to yield a yellow oil (1 g). The crude product was chromatographed and eluted with 20% EtOAc in petroleum ether. The deacylated auxiliary **(105)** (50 mg, 0.18 mmol, 24%) was collected. The pure product **(139)** (203 mg, 0.47 mmol, 64%) was collected as a white solid. R_f 0.55 (20% EtOAc in petroleum ether); m.p. 133-135°C; ν_{max}/cm^{-1} 1778 (urethane, N-CO-O), 1692 (MeCH(Bn)C=O-N), 1604 (Ar); (Found: C, 75.1; H, 6.4; N, 3.2. Calc. for $C_{27}H_{27}NO_4$: C, 75.5; H, 6.3; N, 3.3%); δ_H (270MHz, $CDCl_3$) 7.44-7.17 (10 H, m, $CH_2\underline{Ph}$, $OCH_2\underline{Ph}$), 6.93 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.86 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.02 (2 H, s, $OC\underline{H}_2Ph$), 4.65-4.58 (1 H, m, α-C$\underline{H}$), 4.20-4.06 [3 H, m, $CH_3C\underline{H}(Bn)C=O$, $C\underline{H}_2O$], 3.15 [1 H, dd, *J* 13, 8, $CH_3CH(C\underline{H}_2Ph)C=O$], 2.97 (1 H, dd, *J* 14, 3, β-$C\underline{H}_2$), 2.67 [1 H, dd, *J* 13, 8, $CH_3CH(C\underline{H}_2Ph)C=O$], 2.52 (1 H, dd, *J* 14, 9, β-$C\underline{H}_2$), 1.19 (3 H, d, *J* 7, $C\underline{H}_3CH(Bn)C=O$); δ_C (100MHz, $CDCl_3$) 176.5 [C,

$CH_3CH(Bn)\underline{C}=O]$, 158.0 (C), 153 (C), 139.2 (C), 136.8 (C), 130.4 (CH), 129.3 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 127.2 (C), 126.4 (CH), 115.2 (CH), 69.9 (CH_2, $O\underline{C}H_2Ph$), 65.8 (CH_2, $\underline{C}H_2O$), 55.1 (CH, α-$\underline{C}H$), 39.8 [CH_2, $CH_3CH(\underline{C}H_2Ph)C=O$], 39.6 [CH, $CH_3\underline{C}H(Bn)C=O$], 36.7 ($CH_2$, β-$\underline{C}H_2$), 16.8 [$CH_3$, $\underline{C}H_3CH(Bn)C=O$]; $[\alpha]_D^{20}$ +41 (*c* = 1 in DCM).

(4*S*)-3-Benzyl-4-(4-benzyloxybenzyl)-2-oxazolidinone **(140)** (23 mg, ~8%) was also recovered but contaminated with traces of **(130)**.

(4S)-3-Benzyl-4-(4-benzyloxybenzyl)-2-oxazolidinone **(140)**

m/z (FAB+) 374.3 (MH+, 58%); δ_H (400 MHz, $CDCl_3$) 7.43 (8H, m, $NCH_2\underline{Ph}$, $OCH_2\underline{Ph}$), 7.26-7.22 (2H, m, CH, $CH_2\underline{Ph}$), 6.94 (2H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.87 (2H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.01 (2H, s, $CH_2\underline{Ph}$), 4.83 (1H, d, *J* 15, $NC\underline{H}_2Ph$), 4.09 (1H, d, *J* 15, $NC\underline{H}_2Ph$), 4.05-4.11 (1H, m, $C\underline{H}_2O$), 3.97 (1H, dd, *J* 9, 6, $C\underline{H}_2O$), 3.80-3.65 (1H, m, α-CH), 3.00 (1H, dd, *J* 14, 4, β-CH_2), 2.56 (1H, dd, *J* 14, 7, β-CH_2).

After cleavage, the auxiliary **(105)** was recovered in 78% yield while the α-benzylated propionic acid **(136)** was recovered in 89%.

General procedure for the alkylation of (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone **(130)** *with alkyl halides*

LDA (1.5 M in hexane, 0.43 ml, 0.65 mmol) was added to stirred solution of *N*-propionylated auxiliary **(130)** (200 mg, 0.59 mmol) in dry THF (2 ml) at 0°C under N_2 atmosphere. After 30 min., alkyl halide was added. The solution was agitated for 30 min. before warming to r.t. and stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 ml). The crude product was obtained after an extractive workup and solvent removal.

Part a: *Methyl iodide as alkylating reagent*

Methyl iodide (0.18 ml, 2.89 mmol) was used. The crude product (281 mg) was purified with column chromatography (20% EtOAC in petroleum ether). The deacylated auxiliary **(105)** (73 mg) was collected in 44%. The pure compound **(138)** (33 mg) was recovered in 16% yield.

(4S)-4-(4-Benzyloxybenzyl)-3-[(2R)-2-methyl-1-oxopropyl]-2-oxazolidinone **(138)**

R_f 0.39 (20% EtOAc in petroleum ether); m.p. 112-114°C; δ_H (270MHz, $CDCl_3$) 7.45-7.32 (5 H, m, $OCH_2\underline{Ph}$), 7.12 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 6.93 (2 H, d, *J* 9, $C_6\underline{H}_4OBn$), 5.04 (2 H, s, $OC\underline{H}_2Ph$), 4.67-4.58 (1 H, m, α-C$\underline{H}$), 4.24-4.13 (2 H, m, C$\underline{H}_2O$), 3.18 (1 H, dd, *J* 13, 3, β-C$\underline{H}_2$), 3.15 [1 H, heptat, *J* 7, $CH_3C\underline{H}(CH_3)C{=}O$], 2.72 (1 H, dd, *J* 13, 9, β-C$\underline{H}_2$), 1.23 [3 H, d, *J* 7, $CH(C\underline{H}_3)_2C{=}O$], 1.19 (3 H, d, *J* 7, $CH(C\underline{H}_3)_2C{=}O$); δ_C (100MHz, $CDCl_3$) 177.7 (C, $CH_3CH(CH_3)\underline{C}{=}O$), 158.1 (C), 153 (C), 136.8 (C, $OCH_2\underline{Ph}$), 130.5 (CH, $\underline{C}_6H_4OBn$), 128.6 (CH, $OCH_2\underline{Ph}$), 128.0 (CH, $OCH_2\underline{Ph}$), 127.5 (CH, $OCH_2\underline{Ph}$), 115.2 (CH, $\underline{C}_6H_4OBn$), 70.0 (CH_2, $O\underline{C}H_2$ Ph), 66.1 (CH_2, $\underline{C}H_2O$), 55.4 (CH, α-$\underline{C}$H), 39.6 [CH, $CH_3\underline{C}H(Bn)C{=}O$], 37.0 ($CH_2$, β-$\underline{C}H_2$), 32.6 [CH, $\underline{C}H(CH_3)_2C{=}O$], 19.2 [$CH_3$, $CH(\underline{C}H_3)_2C{=}O$], 18.7 [$CH_3$, $CH(\underline{C}H_3)_2C{=}O$]; *m/z* (FAB+): 354.2 ($MH^+$, 63%). *m/z* (acc. mass FAB+): Found M^+, 354.17053 required $C_{21}H_{24}NO_4$ 354.17053; ν_{max}/cm^{-1} 1779 (urethane, O-C=O-N), 1702 [$CH_3CH(CH_3)C{=}O$], 1610 (Ar).

General procedure **[286]** *for the alkylation of (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone* **(130)** *with reverse addition of base and alkyl halides*

Alkyl halide (1.2 eq.) was added to a stirred solution of *N*-propionylated auxiliary **(130)** (80 mg, 0.24 mmol) in dry THF (1 ml) at specific temperature under N_2

atmosphere. LiHMDS (1 M in THF, 0.25 ml, 0.25 mmol) was added soon afterward. The solution was warmed to r.t. and stirred for 16 h. Water (4 ml) was added to the reaction mixture and then extracted with dichloromethane (2 x 10 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent removed to furnish the crude product.

Part a: *With benzyl bromide and at -78 °C*

Benzyl bromide (30 µl, 0.25 mmol) was used. The crude mixture (232 mg) was chromatographed and eluted with 15% EtOAc in petroleum ether. Pure crystalline product **(139)** (72 mg, 0.17 mmol, 71%), *N*-benzylated **(140)** (8 mg, 9%) and deacylated material **(105)** (2 mg, 3%) were collected.

Part b: *With benzyl bromide and at 0°C*

Benzyl bromide (30 µl, 0.25 mmol) was used. The crude mixture (220 mg) was chromatographed and eluted with 15% EtOAc in petroleum ether. Pure crystalline product **(139)** (63 mg, 0.15 mmol, 62%), *N*-benzylated **(140)** (16 mg, 18%) and deacylated material **(105)** (5 mg, 7%) were collected.

The auxiliary **(105)** was recovered in 95% yield after the removal of the acid derivatives. The α-benzylated propionic acid **(136)** was recovered in 86% yield.

The α-benzylation of (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone **(130)** *in the presence of lithium chloride*

Anhydrous lithium chloride (20 mg, 0.47 mmol) was heated in vacuo before cooling under N_2 atmosphere. A solution of oxazolidin-2-one **(130)** (80 mg, 0.24 mmol) in dry THF (2 ml) was cannulated into this mixture. The solution was cooled to 0°C and LDA (2 M in heptane, 120 µl, 0.24 mmol) was added. After 30 min. at 0°C,

benzyl bromide (140 μl, 1.18 mmol) was syringed into the stirred solution under N_2 atmosphere. The reaction mixture was stirred at 0°C for 30 min., r.t. for 30 min. and quenched with saturated ammonium chloride solution (2 ml). The reaction mixture was partitioned between water (10 ml) and dichloromethane (15 ml). The aqueous layer was separated and extracted with dichloromethane (2 x 15 ml). The organic layers were combined, dried (Na_2SO_4), filtered and solvent removed to yield a yellow oil (400 mg). The crude mixture was chromatographed and eluted with 15% EtOAc in petroleum ether to afford the product **(139)** in 23 mg (23%). The deacylated auxiliary **(105)** was recovered in 72% (48 mg, 0.17 mmol).

The benzylation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)** *in the presence of dimethylpropyleneurea (DMPU)*

LDA (1.5 M in hexane, 0.93 ml, 1.40 mmol) was added to a stirred solution of *N*-acylated oxazolidinone **(123)** (500 mg, 1.36 mmol) in dry THF (4 ml) and dimethylpropyleneurea (490 μl, 4.05 mmol) at 0°C under N_2 atmosphere. The solution was stirred for 30 min. before benzyl bromide (810 μl) was added. The mixture was agitated for 30 min. and then warmed to r.t. and stirred for further 50 min. Saturated ammonium chloride solution (4 ml) was used to quenched the reaction. The aqueous layer was separated and extracted with dichloromethane (5 x 10 ml). The organic layers were combined, dried (Na_2SO_4), filtered and solvent removed to yield a yellow oil (1.74 g). The crude mixture was chromatographed and eluted with 15% EtOAc in petroleum ether to afford the product **(124)** (120 mg, 19%) as a white solid. The starting material **(123)** (110 mg, 22%) and *N*-benzylated product **(125)** (153 mg, 28%) were also collected.

The auxiliary was recovered in 99% (81 mg) yield after treatment with lithium hydroperoxide. The chiral (*R*)-2-methyl-3-phenylpropionic acid **(136)** was collected in quantitative yield (43 mg) with $[\alpha]_D^{18}$ -22.3 *c* = 0.99 in $CHCl_3$; Lit**[323]**$[\alpha]_D^{20}$ -23.1 *c* = 1 in $CHCl_3$.

The attempted tert-butyldimethylsilylation of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)** *using tert-butyldimethylsilyl triflate***[301]** *as silylating reagent*

tert-Butyldimethylsilyl triflate (94 µl, 0.41 mmol) was syringed to a solution of *N*-propionyloxazolidinone **(123)** (100 mg, 0.27 mmol) in dry deuterated dichloromethane (1 ml) with stirring at r.t.. Triethylamine (45 µl, 0.33 mmol) was then added. The solution was stirred at r.t. for 16 h under N_2 atmosphere. The colour of the mixture changed from colourless to pale yellow then brownish orange during this period. ^{1}H NMR spectrum of the crude mixture did not showed the vinylic proton of the product.

The attempted aldol reaction of [4S,(Z)]- 4-(4-benzyloxybenzyl)-5,5-dimethyl-3-{1-{[(1,1-dimethylethyl)dimethylsilyl]oxyl}-1-propenyl}-2-oxazolidinone **(123)** *with benzaldehyde*

tert-Butyldimethylsilyl triflate (94 µl, 0.41 mmol) was syringed to a solution of *N*-propionyloxazolidinone **(123)** (100 mg, 0.27 mmol) in dry deuterated dichloromethane (1 ml) with stirring at r.t. under N_2 atmosphere. Triethylamine (45 µl, 0.33 mmol) was then added. The solution was stirred at r.t. for 16 h before cooled to -40°C. A solution of benzaldehyde (33 µl, 0.33 mmol) in dried

dichloromethane (1 ml) was syringed into the mixture. After 30 min. at -40°C, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (2 ml). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to yield an yellow oil (200 mg). Purification with chromatography (16% EtOAc in hexane) recovered the starting auxiliary and aldehyde as mixed fractions as well as the *O*-deprotected material **(143)** (23 mg).

The attempted silylation (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)**

Part a: *Trimethylsilylation*

LDA (1.5 M in hexane, 93 µl, 0.14 mmol) was added dropwise into a stirred solution of *N*-propionyloxazolidinone **(123)** (50 mg, 0.14 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere. After 30 min., redistilled trimethylchlorosilane (52 µl, 0.41 mmol) was syringed into the reaction mixture. The yellow colour of the mixture paled upon the addition of the silylating reagent. The solution was kept at 0°C for 30 min. and at r.t. for 35 min. The solvent was removed *in vacuo* and the yellow oil obtained was dissolved in deuterated DMSO. ^{1}H NMR spectrum of the crude mixture did not showed the vinylic proton of the product.

Part b: *Tert-butyldimethylsilylation*

LDA (1.5 M in hexane, 93 µl, 0.14 mmol) was added dropwise into a stirred solution of *N*-propionyloxazolidinone **(123)** (50 mg, 0.14 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere. After 30 min., *tert*-butyldimethylsilyl chloride (62 mg, 0.41 mmol) in dry THF (1 ml) was added to the solution and then stirred at 0°C for 30 min. The mixture was warmed to r.t. and stirred for further 30 min. The solvent was

removed *in vacuo* and the residue was dissolved in deuterated chloroform. ^{1}H NMR spectrum and electron spray mass spectrum indicated the absence of product.

Part c: *Tert-butyldiphenylsilylation*

i) *With LDA as base*

LDA (1.5 M in hexane, 93 µl, 0.14 mmol) was added into a stirred solution of *N*-propionyloxazolidinone **(123)** (50 mg, 0.14 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere. After 30 min., *tert*-butyldiphenylsilyl chloride (110 µl, 0.42 mmol) in dry THF (1 ml) was added to the solution and then stirred at 0°C for 30 min. The mixture was warmed to r.t. and stirred for further 30 min. The solvent was removed *in vacuo* and the residue was dissolved in deuterated dimethylsulfoxide. ^{1}H NMR spectrum showed two new doublets in the δ 6.1-δ 6.8 region.

ii) *With sodium bis(trimethylsilyl)amide as base*

Same procedure as i) except sodium bis(trimethylsilyl)amide was used instead of LDA. ^{1}H NMR spectrum of the crude mixture also showed the two new doublets in the δ 6.1-δ 6.8 region.

iii) *Larger scale reaction using LDA as base*

Same procedure as i) except the reaction was repeated on a 200 mg scale. 25% of the reaction mixture by volume was taken for NMR analysis which indicated the presence of the new compound. The rest of the reaction mixture was subjected to rotatory evaporation which furnished an oil (580 mg). The crude product was chromatographed and eluted with 10% EtOAc in petroleum ether. Starting material **(123)** (56 mg, 28%) was recovered. Impure deacylated oxazolidinone **(90)** (104 mg) was also recovered. The product **(145)** (14 mg) was collected contaminated with starting material.

[4S,(Z)]- 4-(4-Benzyloxybenzyl)-5,5-dimethyl-3-{1-{[(1,1-dimethylethyl)diphenylsilyl]oxyl}-1-propenyl}-2-oxazolidinone **(145)**

δ_H (400 MHz, $CDCl_3$) 7.77-7.66 (4 H, m, *t*-BuSi*Ph*$_2$), 7.60-7.30 (12 H, m, *t*-BuSi*Ph*$_2$, OCH_2*Ph*, C*H*-C=C), 6.61 (2 H, d, *J* 9, C_6H_4OBn), 6.07 (2 H, d, *J* 9, C_6H_4OBn), 4.92 (2 H, s, OCH_2Ph), 3.45 (1 H, dd, *J* 12, 2, α-C*H*), 2.73 (1 H, dd, *J* 15, 12, β-CH_2), 2.50 (1 H, d, *J* 15, β-CH_2), 1.41 (3 H, s, vinylic CH_3), 1.38 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 1.24 (9 H, s, *t-Bu*); δ_C (100 MHz, $CDCl_3$) 161 (C, N-*C*=O-O), 83.3 (C, *C*-$(CH_3)_2$-O), 69.9 (CH_2, OCH_2Ph), 67.1 (CH, α-CH), 37.7 (CH_2, β-CH_2), 29.1 (CH_3, *t-Bu*), 28.7 [CH_3, C-(*C*H_3)$_2$], 23.0 [CH_3, C-(*C*H_3)$_2$], 19.8 (CH_3, *C*H_3-C=C). R_f 0.21 (10% EtOAc in petroleum ether).

The attempted α-benzylation of [4S,(Z)]- 4-(4-benzyloxybenzyl)-5,5-dimethyl-3-{1-{[(1,1-dimethylethyl)dimethylsilyl]oxyl}-1-propenyl}-2-oxazolidinone **(142)**

LDA (1.5 M in cyclohexane, 0.36 ml, 0.54 mmol) was syringed to a solution of *N*-acylated oxazolidinone **(123)** (200 mg, 0.54 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere. After 30 min., *tert*-butyldimethylchlorosilane (90 mg, 0.60 mmol) in dry THF (1 ml) was added and stirred for 45 min. at 0°C. Benzyl bromide (320 µl, 2.69 mmol) was then added. The solution was kept at 0°C for 30 min. then r.t. for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 ml). The mixture was extracted with EtOAc (3 x 15 ml) and the organic layers were combined, dried (Na_2SO_4), filtered and solvent evaporated to yield a yellow oil (215 mg). TLC of the crude mixture showed the presence of a large amount of starting material. Deacylated oxazolidinone was also detected. No alkylated product was detected.

Titanium tetrachloride catalysed aldol reaction between benzaldehyde and [4S,(Z)]-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-{1-{[(1,1-dimethylethyl)dimethylsilyl]oxyl}-1-propenyl}-2-oxazolidinone **(142)**

LDA (1.5 M in cyclohexane, 0.91 ml, 1.37 mmol) was added to a stirred solution of *N*-acylated auxiliary **(123)** (500 mg, 1.36 mmol) in dry THF (2 ml) at 0°C under N_2 atmosphere. After 30 min., a solution of *tert*-butyldimethylchlorosilane (246 mg, 1.63 mmol) in dry THF (1 ml) was syringed into the reaction mixture. The solution was agitated at 0°C for 30 min. and r.t. for 30 min. before removal of solvent *in vacuo*. The yellow residual solid was redissolved in dry dichloromethane (2 ml) and cooled to -78°C.

This mixture was cannulated into a solution of benzaldehyde (126 µl, 1.24 mmol) and titanium tetrachloride (1 M in DCM, 1.24 ml, 1.24 mmol) in dry dichloromethane (1 ml) at -78°C under N_2 atmosphere. The colour of solution changed to orange after the addition. The reaction mixture was kept at -78°C for 10 min. before quenching with saturated aqueous NH_4Cl (3 ml). The mixture was extracted with Et_2O (2 x 25 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent evaporated to yield a yellow solid (314 mg). The crude mixture was chromatographed and eluted with 10% EtOAc in petroleum. Starting material **(123)** (143 mg) were recovered as the only major component. Trace of deacylated auxiliary **(90)** were detected but not collected.

The attempted non-catalysed aldol reaction of benzaldehyde and (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)**

LDA (1.5 M in cyclohexane, 0.36 ml, 0.54 mmol) was syringed to a solution of *N*-acylated oxazolidinone **(123)** (200 mg, 0.54 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere with stirring. After 30 min., benzaldehyde (83 µl, 0.82 mmol) was added and stirred for 30 min. at 0°C then 30 min. at r.t. before quenching with saturated aqueous NH_4Cl (2 ml). Extraction of the reaction mixture with EtOAc (3 x 20 ml) was followed by drying (Na_2SO_4) of the organic layers. The solution was filtered and solvent removed to yield a yellow solid (220 mg). TLC (20% EtOAC in petroleum ether) indicated a large amount of unreacted starting material **(123)** and deacylated product **(90)**.

The attempted α-deuteration of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)**

Part a: *With temperature at 0°C*

LDA (1.5 M in hexane, 146 µl, 0.22 mmol) was added dropwise into a stirred solution of *N*-propionyloxazolidinone **(123)** (80 mg, 0.22 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere. The solution was agitated for 45 min. and deuterium oxide (1 ml) was added. The reaction mixture was warmed to r.t. and stirred for 30 min. The organic solvent was removed and the aqueous layer was extracted with EtOAc (2 x 10 ml). The extracts were combined, dried ($MgSO_4$), filtered and solvent removed to furnish a pale yellow oil (60 mg). ^{1}H NMR spectrum of the crude mixture did not showed sign of deuterium incorporation. Peaks simplification were not observed.

Part b: *With temperature at -10°C*

Same procedure as above. The reaction was carried out on 50 mg scale and the enolisation was carried out at -10°C instead. The ^{1}H NMR spectrum of the crude mixture did not showed sign of deuterium incorporation.

The attempted α-benzylation of zinc enolate **[304]** *derived from (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone* **(130)**

Part a: *Under standard conditions*

LDA (2 M in THF/heptane, 0.12 ml, 0.24 mmol) was added to a stirred solution of *N*-acylated auxiliary **(130)** (80 mg, 0.24 mmol) in dry THF (1 ml) at 0°C under N_2 atmosphere. After 30 min., solution of zinc bromide (54 mg, 0.24 mmol) in dry THF (1 ml) was cannulated into the reaction mixture and stirred for 10 min. The solution became yellow and slightly cloudy. Benzyl bromide (0.14 ml, 1.18 mmol) was syringed into the mixture and kept for 30 min. at 0°C then r.t.. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 ml). The mixture was extracted with dichloromethane (2 x 10 ml). The combined organic layer was dried (Na_2SO_4), filtered and solvent removed to furnish a yellow oil (331 mg). The crude mixture was chromatographed and eluted with 20% EtOAc in petroleum ether. Starting auxiliary **(130)** (40 mg, 50 %) and deacylated auxiliary **(105)** (32 mg, 0.113 mmol, 48%) were also recovered. No product was detected.

Part b: *With longer reaction time*

Same procedure as Part a) except the following condition was changed. The reaction mixture was stirred for 6 h at 0°C instead of 30 min. After workup, a crude mixture (401 mg) was obtained and purified using column chromatography using 20%

EtOAc in petroleum ether. No product was collected. Starting material **(130)** (44 mg, 55%) was also recovered.

The attempted α-benzylation of boron enolate **[305]** *derived from (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone* **(130)** *in the presence of zinc bromide*

Part a: *Using triethylamine and n-dibutylboryl triflate*

n-Dibutylboryl triflate (1 M in DCM, 0.28 ml, 0.28 mmol) was syringed dropwise into a stirred solution of *N*-acyloxazolidinone **(130)** (80 mg, 0.24 mmol) in dry dichloromethane under N_2 atmosphere at 0°C. The solution turned yellow as the boron reagent was added. Dry triethylamine (43 µl, 0.31 mol) was then added straight afterward. The reaction mixture was kept at 0°C for 2 h before zinc bromide (54 mg, 0.24 mmol) in 1:1 dry THF/dichloromethane (1.6 ml) and benzyl bromide (0.14 ml, 1.18 mmol) were added. The mixture was agitated for 30 min. at 0°C then 30 min. for r.t.. The reaction mixture was quenched with saturated aqueous NH_4Cl (1.5 ml) and partitioned between water (8 ml) and dichloromethane (10 ml). The aqueous layer was extracted with more dichloromethane (2 x 10 ml). The combined organic layer was washed with 2 M hydrochloric acid (10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and water (10 ml). The extract was dried (Na_2SO_4), filtered and solvent removed to yield a yellow solid (450 mg). Starting material **(130)** (66 mg, 83%) was recovered after the crude mixture was chromatographed.

Part b: *Using longer reaction time*

Same procedure as Part a) except the following condition had been altered. The reaction mixture was stirred at 3 h after the addition of benzyl bromide. After usual workup, a yellow oil (473 mg) was obtained. Starting material **(130)** (67 mg, 84%) was recovered after column chromatography.

Part c: *With diisopropylamine and n-dibutylboryl triflate*

Same as Part a) except diisopropylamine (53 µl, 0.31 mmol) was used instead of triethylamine. A yellow oil (429 mg) was obtained after workup. Starting material **(130)** (76 mg, 95%) was recovered after chromatography.

The attempted α-benzylation of tin(II) enolate **[324]** *derived from (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone* **(130)**

Part a: *Under standard conditions*

N-propionyloxazolidinone **(130)** (100 mg, 0.27 mmol) in dry THF (1 ml) was stirred with *N*-ethylpiperidine (56 µl, 0.41 mmol) at r.t. for 5 min. before cooled to -5°C. This mixture was cannulated into a solution of tin (II) triflate (146 mg, 0.35 mmol) in dry THF (1 ml) at -5°C under N_2 atmosphere. Upon addition, the solution changed to a creamy yellow colour with fine precipitate. This colour paled as the mixture was stirred for 4 h at -5°C. Benzyl bromide (49 µl, 0.41 mmol) in dry THF (1 ml) was added to the solution and kept at -5°C for 2 h. The reaction mixture was poured into a solution containing phosphate buffer solution (pH 7, 15 ml) and EtOAc (15 ml) with stirring. The mixture was filtered through celite and the precipitate was washed with EtOAc (3 x 15 ml). The combined organic extract was washed with brine (15 ml), dried (Na_2SO_4), filtered and solvent removed to give an oil with white

precipitate (218 mg). TLC (20% EtOAc in petroleum ether) indicated a lack of reaction. Only starting material **(130)** and benzyl bromide were detected.

Part b: *With diisopropylamine and tin(II) triflate*

A solution of *N*-acyloxazolidinone **(130)** (80 mg, 0.24 mmol) in dry dichloromethane (1 ml) was added to a mixture of diisopropylethylamine (40 μl, 0.24 mmol) and tin (II) triflate (100 mg, 0.24 mmol) in THF/DCM (1:1, 1 ml) at 0°C under nitrogen atmosphere. The solution was stirred for 3 h at 0°C before cannulating a solution of zinc bromide (54 mg, 0.24 mmol) in THF followed by benzyl bromide (140 ml, 1.18 mmol). The mixture was agitated for 30 min. at 0°C then 30 min. at r.t. The reaction mixture was quenched by decanting into a solution of KF (0.25 M, 15 ml) and ethyl acetate (20 ml) and stirred for 30 min. After separation, the organic layer was filtered through a samll pad of celite. The ethyl acetate layer was then dried, filtered and the solvent removed to yield a yellow solid (287 mg). Starting material **(130)** (66 mg, 91%) was recovered after the crude mixture was chromatographed.

Part c: *Using LDA as base*

LDA (2 M in THF/heptane, 0.12 ml, 0.24 mmol) was syringed into a solution of acylated auxiliary **(130)** (80 mg, 0.24 mmol) in dry THF (1.5 ml) under N_2 atmosphere at -5°C with stirring. After 30 min., tin triflate (104 mg, 0.25 mmol) in dry THF (1 ml) was added to the reaction mixture and agitated for 10 min. Benzyl bromide (0.14 ml, 1.18 mmol) was added to the solution and kept at -5°C for 30 min. then at r.t. for 30 min. A yellow precipitate was formed during this period. The reaction mixture was decanted into a solution of aqueous ammonium flouride (0.25 M, 15 ml) and EtOAc (15 ml) and vigorously stirred for 30 min. A white precipitate formed during the agitation was filtered. The organic layer was separated and

washed with water (2 x 10 ml), brine (10 ml), dried (Na_2SO_4), filtered and solvent removed to furnish a yellow oil (418 mg). The crude mixture was chromatographed with 20% EtOAc in petroleum ether. Starting material **(130)** (53 mg, 66%) contaminated with tin residue was recovered. Deacylated auxiliary **(105)** (4 mg, 6%) was also collected. No product was detected.

The α-benzylation of tin(IV) enolate **[325]** *derived from (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone* **(130)**

Part a: *With 1 eq. of tin(IV) reagent*

LDA (2 M in THF/heptane, 0.12 ml, 0.24 mmol) was syringed into a solution of acylated auxiliary **(130)** (80 mg, 0.24 mmol) in dry THF (1.5 ml) under N_2 atmosphere at 0°C with stirring. A solution of triphenyltin chloride (93 mg, 0.24 mmol) in dry THF (1 ml) was added after 30 min. The solution was stirred for 10 min. and benzyl bromide (0.14 ml, 1.18 mmol) was added. The reaction mixture was kept at 0°C for 30 min. then at r.t. 30 min. The reaction mixture was decanted into a solution of aqueous ammonium fluoride (0.25 M, 15 ml) and EtOAc (15 ml) and vigorously stirred for 30 min. The solution was filtered and the organic layer was separated and washed with water (2 x 10 ml), brine (10 ml), dried (Na_2SO_4), filtered and solvent removed to furnish a yellow oil (300 mg). TLC (20% EtOAC in petroleum ether) of the crude product indicated the presence of product **(139)** and the complete consumption of starting material **(130)**. The crude mixture was not purified.

Part b: *With 0.4 eq. of tin(IV) reagent*

Same procedure as Part a) except the following condition had been altered. The number of equivalent of triphenyltin chloride (34 mg, 0.09 mmol) used was reduced to 0.4 equivalent. The reaction mixture was decanted into a solution of aqueous sodium hydroxide (1 M, 10 ml) and EtOAc (10 ml) and vigorously stirred for 1 h. The solution was filtered. The organic layer was separated and washed with brine (10 ml), dried (Na_2SO_4), filtered and solvent removed to furnish a viscous yellow oil (348 mg). Chromatographic purification of the crude product eluted with 20 % EtOAc in petroleum ether gave the product **(139)** (49 mg, 39%) contaminated with tin residue. TLC of the crude mixture showed the starting material was consumed completely.

The α-benzylation of tin(IV) enolate derived from (4S)-4-(4-benzyloxybenzyl)-3-(1-oxopropyl)-2-oxazolidinone **(130)** *in the presence of a tetraalkylammonium salt*[**307**]

Part a: *Under standard conditions*

LDA (2 M in THF/heptane, 0.15 ml, 0.30 mmol) was added into a solution of acylated auxiliary **(130)** (100 mg, 0.30 mmol) in dry THF (1 ml) under N_2 atmosphere at 0°C with stirring. After 30 min., a solution of triphenyltin chloride (93 mg, 0.24 mmol) in dry THF (1 ml) was added and stirred for 10 min. before tetrabutylammonium bromide (146 mg, 0.43 mmol) in dry THF (2 ml) was introduced into the reaction. Heating and sonication were required to dissolve the ammonium salt in THF. The solution was kept at 0°C for 10 min. and benzyl bromide (170 μl, 1.43 mmol) was syringed into the reaction mixture. The resultant solution was kept at 0°C for 30 min and then at r.t. for 30 min. The reaction mixture

was poured into a mixture of aqueous sodium hydroxide (1 M, 10 ml) and EtOAc (10 ml) with vigorous stirring. After 1 h, the organic layer was separated and washed with brine (10 ml), dried (Na_2SO_4), filtered and solvent removed to yield a yellow oil (360 mg). The crude product was chromatographed and eluted with 20% EtOAc in petroleum ether. Tin contaminated product **(139)** (34 mg, 27%) was collected.

Part b: *Control experiment without the tin(IV) reagent*

Same procedure as Part a) except the following condition was changed. Triphenyltin chloride was not added to the reaction. After quenching with aqueous saturated NH_4Cl (1 ml) and usual extractive workup, a yellow oil (366 mg) was obtained. Chromatographic purification of the crude product eluted with 20% EtOAc in petroleum ether yielded the product **(139)** (30 mg, 0.07 mmol, 30%). Deacylated auxiliary **(105)** (41 mg, 0.236 mmol, 61%) was also recovered.

The attempted 1,4-Michael addition of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)** *to 2-cyclopenten-1-one*

n-Butyl lithium (1.6 M, 150 µl, 0.24 mmol) was added into a stirred solution of diisopropylamine (37 µl, 0.26 mmol) in dry THF (1 ml) at 0°C under Ar atmosphere. After 1 h, a solution of *N*-propionyloxazolidin-2-one **(123)** (80 mg, 0.22 mmol) in dried THF (1.5 ml) was added to the solution and stirred for 30 min. 2-cyclopenten-1-one (22 µl, 0.26 mmol) was added thereafter and the mixture was stirred at 0°C for 30 min. followed by 40 min. at r.t.. The reaction was quenched with saturated ammonium chloride solution (2 ml) and extracted with diethyl ether (4 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered and solvent removed to

yield an oil (130 mg). TLC (20% EtOAc in petroleum ether) detected only starting material **(123)**, enone and deacylated auxiliary **(90)**.

The attempted 1,4-Michael addition of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)** *to 2-cyclopenten-1-one using lithium 2-thienylcyanocuprate as the cyanocuprate precursor*[310]

Part a: *Under standard conditions*

n-Butyl lithium (1.6 M in hexane, 180 µl, 0.29 mmol) was syringed into a stirred solution of diisopropylamine (46 µl, 0.33 mmol) in dry THF (1 ml) at -5°C under N_2 atmosphere. After 1 h, a solution of *N*-propionyloxazolidin-2-one **(123)** (100 mg, 0.27 mmol) in dried THF (1.5 ml) was added to the solution and stirred for 30 min. Lithium 2-thienylcyanocuprate (0.25 M, 1.2 ml, 0.30 mmol) was syringed into the solution and stirred for 2 h at 0°C before cooled to -40°C. 2-cyclopenten-1-one (28 µl, 0.33 mmol) was added to the yellow coloured solution. The resultant mixture was stirred for 2 h. The colour of solution changed to green with precipitate during this period. The temperature was warmed to 0°C and the mixture was stirred for 4 h before quenching with saturated aqueous NH_4Cl (2 ml). The green colour of the solution lightened after quenching. The reaction mixture was extracted with Et_2O (3 x 25 ml). The combined organic layer was dried (Na_2SO_4), filtered and evaporated to yield a brown coloured solid (180 mg). TLC (80:20 petroleum ether/EtOAc) of the crude mixture indicated a lack of reaction.

Part b: *With longer reaction time for organocuprate formation*

Same procedure as Part a) except the following conditions had been changed. Lithium 2-thienylcyanocuprate was stirred with the enolate solution for 4 h at 0°C.

The enone was stirred with the auxiliary derived organocuprate for 2 h at 0°C before quenching. After workup, a brown solid (170 mg) was obtained but TLC showed no sign of reaction.

Part c: *With higher reaction temperature*

Same procedure as Part a) except the following conditions had been changed.

The enolates was reacted with lithium 2-thienylcyanocuprate at 0°C for 35 min., then warmed to r.t. for 10 min before cooling to -40°C. Enone was added and allowed to react with the auxiliary derived organocuprate for 2 h. The temperature was raised to 0°C and the reaction mixture was agitated for further 160 min. TLC of the workup crude material indicated no sign of reaction. Only starting material **(123)**, enone and depropionylated auxiliary **(90)** were detected.

The attempted 1,4-Michael addition of (4S)-4-(4-benzyloxybenzyl)-5,5-dimethyl-3-(1-oxopropyl)-2-oxazolidinone **(123)** *to 2-cyclopenten-1-one using copper(I) cyanide as the cyanocuprate precursor*[**310**]

Part a: *Under standard conditions*

n-Butyl lithium (1.6 M in hexane, 0.19 ml, 0.30 mmol) was syringed into stirred solution of diisopropylamine (46 μl, 0.326 mmol) in dry THF (1 ml) under N_2 atmosphere at 0°C. After 65 min., a solution of *N*-propionyloxazolidin-2-one **(123)** (100 mg, 0.27 mmol) in dry THF (1.5 ml) was cannulated into a suspension of copper cyanide (12 mg, 0.13 mmol) in dry THF (1 ml) at 0°C under N_2. The resultant solution was stirred for 75 min. and 2-cyclopenten-1-one (14 μl, 0.17 mmol) was added. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 ml) after 6 h of agitation. TLC (20% EtOAc in petroleum ether) of the

organic layer showed the presence of starting materials **(123)** and deacylated auxiliary **(90)**.

Part b: *With shorter reaction time*

Same procedure as Part a) except the following condition had been changed. The enolate formation took 45 min. instead of 65 min. The enolate/CuCN mixture was stirred for 90 min. and the resulting cyanocuprate was allowed to react with the enone for 1 h at 0°C. After usual workup, a yellow oil (116 mg) was obtained. TLC of the organic layer indicated only starting material **(123)** and deacylated product **(90)** were present.

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